



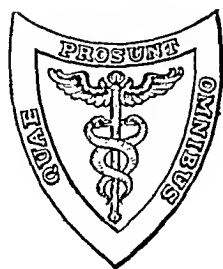
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# CONTENTS OF VOL. CLXXXII

## ORIGINAL ARTICLES

- The Heart in Old Age. A Study of 700 Patients Seventy-five Years of Age and Older. By FREDRICK A. WILLIUS, M.D., Rochester, Minn. 1
- The Treatment of the Gastrocardiac Syndrome (Gastric Cardiopathy). By Privy Counsellor L. ROEMHELD, M.D., Gundelsheim, Germany . 13
- An Anaysis of One Hundred Examples of Cardiac Pain in Private Practice. By LOUIS FAUGÈRES BISHOP, M.D., Sc.D., and LOUIS FAUGÈRES BISHOP, JR., M.D., New York City . . . . . 19
- Rheumatic Fever in Adult Porto Rican Immigrants. By ERNST P. BOAS, M.D., New York City . . . . . 25
- The Case For and Against the Operative Treatment of Angina Pectoris. By WALLACE M. YATER, M.D., and ARTHUR P. TREWHELLA, M.D., Georgetown University . . . . . 35
- A New and Simple Mechanical Retractor for Abdominal Surgery. By JOHN R. O'SULLIVAN, M.D., and BERNARD A. O'CONNOR, M.D., Kearny, N. J. . . . . 43
- The Specific Dynamic Action of Food in Abnormal States of Nutrition. By J. M. STRANG, M.D., H. B. McCLUGAGE, Ph.D., Pittsburgh, Pa., with the technical assistance of M. A. BROWNLEE, R. N. . . . . 49
- Extra-pollen Hypersensitivity—A Most Important Consideration in the Treatment of Hay Fever. By H. HAROLD GELFAND, M.D., New York City . . . . . 81
- Appendicitis in Children. By LESLIE W. TASCHE, M.D., Sheboygan, Wis. 86
- A Unique Anomaly of the Biliary Tract. Communications Between Cystic and Hepatic Ducts with Occlusion of Common Duct and Separate Entrances into the Duodenum. By ANTONIO GENTILE, M.D., University of Virginia . . . . . 95



Toxicity and Rate of Elimination of Organic Arsenicals (Stovarsol and Treparsol) in the Treatment of Endamebiasis. By PHILIP W. BROWN, B.A., M.D., M.S., and ARNOLD E. OSTERBERG, B.S., M.S., Ph.D., Rochester, Minn. . . . .	257
Guides to the Prevention and Treatment of the Simpler Neuroses. By MAURICE FREMONT-SMITH, M.D., Boston, Mass. . . . .	261
Diabetes Mellitus and Its Complications. An Analysis of 827 Cases. By FRANCIS D. MURPHY, M.S., M.D., and GAIL F. MOXON, A.B., M.D., Milwaukee, Wis. . . . .	301
A Study of Five Hundred Diabetics. By ELMER L. SEVRINGHAUS, M.D., Madison, Wis. . . . .	311
Antianemic Influence of Desiccated Whole Hog Stomach. By A. BLAINE BROWER, M.D., F.A.C.P., and WALTER M. SIMPSON, M.D., F.A.C.P., Dayton, Ohio . . . . .	319
The Possible Clinical Indications for Follicular Hormone Therapy Based Upon Its Known Biologic Effect in Animal Experiments. By WALTER SCHOELLER, MAX DOHRN, and WALTER HOHLWEG, Berlin, Germany. . . . .	326
Abnormalities in the White Blood Cell Response. (Leukemoid. Atypical Leukemic and Leukopenic Blood Pictures.) By WILLIAM P. THOMPSON, M.D., New York City . . . . .	334
Pneumoperitoneum in the Treatment of Tuberculous Enterocolitis. By ANDREW L. BANYAI, M.D., Wauwatosa, Wis. . . . .	352
Chronic Basal Nontuberculous Pulmonary Inflammation. Its Etiologic Significance. By HOMER H. CHERRY, M.D., Waverly Hills, Ky. . . . .	367
Tuberculosis Simulating Acute Leukemia. By EUGENE R. MARZULLO, M.D., and J. ARNOLD DE VEER, M.D., Brooklyn, N. Y. . . . .	372
Carbohydrate Metabolism in Relation to Postoperative Crises in Hyperthyroidism. By CHARLES H. FRAZIER, M.D., Sc.D., Philadelphia, Pa. . . . .	378
The Effect of Ephedrin Upon the Human Stomach as Determined Roentgenologically. By WALTER W. FRAY, M.S., M.D., Rochester, N. Y. . . . .	387
A Study of the Five-hour Dextrose Tolerance Curve in Treated Diabetic Patients. By ELAINE P. RALLI, M.D., and JAMES SHANNON, M.D., and ARTHUR STRAUSS, B.A., New York City . . . . .	395
Pseudoneoplastic Luetic Granulomata. By HENRY MILCH, M.D., F.A.C.S., and WALTER GALLAND, M.D., New York City . . . . .	405
Problems of Present-day Gastroenterology. By WALTER C. ALVAREZ, M.D., Rochester, Minn. . . . .	441



Acute Suppurative Parotitis. A Pathologic and Bibliographic Study With Report of Two Cases. By R. P. CUSTER, M.D., Philadelphia	649
A Case of Diabetes Mellitus and Fatty Diarrhea Due to Carcinoma of the Pancreas. Treatment With Very High Carbohydrate Diet and Insulin. THOMAS VANORDEN URMY, M.D., CHESTER MORSE JONES, M.D., and JOSEPHINE COLBURN WOOD, A.B., Boston	662
Jerusalem Artichokes and Liver in the Treatment of Diabetes Mellitus. By SAMUEL SOSKIN, M.D., PH.D., HERBERT F. BINSWANGER, M.D., and SOLOMON STROUSE, M.D., Chicago, Ill.	675
The Rôle of the Streptococcus in Arthritis Deformans. (An Improved Cultural Method). By JOHN W. GRAY, M.D., and CECIL H. GOWEN, Newark, N. J.	682
A Study of 503 Cases of Pulmonary Tuberculosis With Indefinite or No Usual Abnormal Physical Signs. By LAWRASON BROWN, M.D., Saranac Lake, N. Y.	700
Observations on the Etiologic Relationship of Achylia Gastrica to Per- nicious Anemia. IV. A Biologic Assay of the Gastric Secretion of Patients With Pernicious Anemia Having Free Hydrochloric Acid and that of Patients Without Anemia or With Hypochromic Anemia Having no Free Hydrochloric Acid, and of the Rôle of Intestinal Impermeability to Hematopoietic Substances in Pernicious Anemia. By WILLIAM B. CASTLE, M.D., CLARK W. HEATH, M.D., and MAU- RICE B. STRAUSS, M.D., Boston, Mass.	741
Hodgkin's Disease of Bone Marrow and Spleen Without Apparent Involvement of Lymph Nodes. By E. B. KRUMBHAAR, Philadelphia	764
Cardiac Pain and Sudden Death. By ALEXANDER LAMBERT, M.D., New York	769
Concerning Certain Phases of Angina Pectoris Based on a Study of 350 Cases. By HARLOW BROOKS, New York City	784
Experimental Chronic Hyperparathyroidism. I. Metabolism Studies in Man. By J. L. JOHNSON, and R. M. WILDER, Chicago, Ill.	800
Diabetic Pyorrhea. By JOHN BELL WILLIAMS, PH.G., D.D.S., F.A.C.D., Richmond, Va.	807
Immune Transfusion in Lobar Pneumonia. By ALVAN L. BARACH, M.D., With the Technical Assistance of MAX SOROKA, New York City	811
The Cholagogue Effect of the Intravenous Injection of Sodium Dchydro- cholate, With a Résumé of Literature on Bile Salt Metabolism. By ROBERT F. STERNER, B.S., M.D., HENRY J. BARTLE, B.S., M.D., and B. B. VINCENT LYON, A.B., M.D., Sc.D.	822

A Survey of Diphtheria Prevention in Philadelphia. By EDWARD L. BAUER, M.D., Philadelphia, Pa. . . . .	839
Clinical Observations on the So-called Leather-bottle Stomach. By JULIUS FRIEDENWALD, M.D., and THEODORE H. MORRISON, M.D., Baltimore, Md. . . . .	847

## REVIEWS

Reviews of Books . . . . .	119, 268, 412, 566, 708, 859
Books Received . . . . .	126, 277, 417, 571, 714, 963

## PROGRESS OF MEDICAL SCIENCE

Medicine . . . . .	128, 279, 419, 573, 716, 865
Surgery . . . . .	130, 280, 420, 574, 718, 866
Therapeutics . . . . .	132, 282, 422, 577, 720, 868
Pediatrics . . . . .	134, 283, 424, 579, 722, 869
Dermatology and Syphilis . . . . .	137, 286, 427, 581, 724, 871
Gynecology and Obstetrics . . . . .	139, 287, 428, 583, 726, 872
Ophthalmology . . . . .	289, 429, 727, 873
Oto-Rhino-Laryngology . . . . .	141, 430, 730
Radiology . . . . .	142, 291, 431, 584, 730, 875
Neurology and Psychiatry . . . . .	145, 293, 434, 587, 733, 876
Pathology and Bacteriology . . . . .	146, 296, 436, 590, 735, 877
Hygiene and Public Health . . . . .	149, 298, 438, 593, 738, 879
Physiology . . . . .	152, 880







HOBART AMORY HARE. B.Sc., M.D., LL.D.

THE death of Dr. Hobart Amory Hare, early on the morning of June 15, 1931, closed a career of distinguished merit. Born in Philadelphia sixty-eight years ago, son of Bishop William Hobart Hare and Mary Amory Howe Hare, he came of a long line of ancestors eminent not alone in the church, but also in the realm of applied science, from whom he inherited a rich mental endowment.

Following a preparatory education at the Episcopal Academy of Philadelphia, he entered the University of Pennsylvania, was graduated in Medicine in 1884, received the degree of B.S. in 1885, and soon thereafter went abroad and pursued studies at Berne, Leipsic and London, chiefly concerned with physiologic research.

Shortly after his return, well equipped for the position, he was appointed Lecturer in Physiology in the Biological Department of the University of Pennsylvania and began his admirable activities along the lines of original research, especially related to the physiologic action of drugs, and speedily demonstrated his unusual ability in this field of scientific endeavor.

His aptitude for research work became evident even in his student days, in that on his graduation he was awarded the Faculty Prize for his thesis "The Influence of Quinin on the Blood." During the first six years after his graduation he was thrice the recipient of the Fiske Fund Prize of the Rhode Island Medical Society, won the Boylston Prize of Harvard ("Fever and Drugs Which Control It"), divided with Dr. Edward Martin the Cartwright Prize ("Studies in Respiration"), and the Warren Triennial Prize of the Massachusetts General Hospital ("Intestinal Obstruction"), and with Dr. Christian, of France, the prize offered by the Royal Academy of Belgium for a "Treatise on the Pathology and Treatment of Epilepsy," and had the unique honor of receiving the Fothergillian Gold Medal of the Medical Society of London for his essay on "Mediastinal Disease," being the only American who has ever obtained this distinction.

Even at this early period of his career the clinical side of medicine attracted his attention, and his attainments in this respect were recognized by the University of Pennsylvania in his appointment in 1890 as Clinical Professor of Diseases of Children.

One year later he was called by the authorities of the Jefferson Medical College of Philadelphia to fill the chair of Therapeutics and Materia Medica, later enlarged by his selection as Professor of Clinical Medicine and as Physician to the Jefferson Hospital.

For forty years he fulfilled the duties of these positions with an ability unexcelled during that period by any member of the medical staff of this distinguished Institution, as thousands of her alumni who were the happy beneficiaries of his instruction will readily attest.

As one of the editors, first of the University Medical Magazine, later, for a brief period, of The Medical News of Philadelphia, and

subsequently, for many years, of the *Therapeutic Gazette*, he displayed in his editorials his happy faculty of careful appraisal of clinical observations and therapeutic values. He was also editor, since its foundation in 1899, of *Progressive Medicine*, published by the same firm as publishes this journal, a quarterly digest which has been most useful and educationally valuable to the English-speaking medical world.

As a teacher, blessed with a facility and clarity of expression, he held his student audiences in rapt attention as he expounded the physiologic action of drugs and the various indications for their employment in the cure and amelioration of disease, and practically demonstrated their value in his rich clinical service at the Hospital.

Speedily he established his reputation as a consultant. Skillful in his physical examinations, accurate in his analyses of the symptoms-complex, wise in his therapeutic recommendations based on his unusual knowledge of the physiologic action of remedial agents, his services were in constant demand.

In spite of his crowded hours as editor, teacher, practitioner and consultant, Dr. Hare found time to write a number of sterling books and monographs, to edit systems of composite authorship and to make numerous important contributions to current medical literature, representing a product of distinguished work which is little short of amazing. Of these his "*Practical Therapeutics*" and his "*Practical Diagnosis*" achieved the greatest success, the former passing through twenty-two and the latter through nine editions in order to satisfy the universal demand.

His distinguished services in the domain of medicine were emphasized by the Trustees of the University of Pennsylvania in the bestowal of the honorary degree of LL.D. in 1900. He was President of the College of Physicians of Philadelphia, 1925-1927.

As a member of the Board of City Trusts he displayed an ability in comprehending the extensive business interests of this important Committee which commanded the lasting admiration of his colleagues. Deeply interested in Girard College and Wills Hospital, his efforts in their behalf yielded results of high importance.

During the Great War he served his country with fine fidelity as Lieutenant Commander in the Navy.

Dr. Hare's career demonstrated the inestimable value of laboratory training, research and the spirit of research in laying the foundation for a teacher of the art and science of medicine, for a sound practitioner, and for a safe and well-informed consultant. To all these tasks, faithfully performed, he lent a new vitality. He believed thoroughly in his mission: to train medical students for their careers to be devoted to the relief of human suffering and the prolongation of human life. His own life he lived abundantly; he gave richly of the best that was in him. He set his distinctive mark on our science. He will be missed as few men are.

G. E. DE SCHWEINITZ.

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JULY, 1931

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ORIGINAL ARTICLES.

THE HEART IN OLD AGE.\*

A STUDY OF 700 PATIENTS SEVENTY-FIVE YEARS OF AGE  
AND OLDER.

BY FREDRICK A. WILLIUS, M.D.,

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ROCHESTER, MINN.

In a period of sixty-five years fifteen years have been added to the span of life. This prolongation of life has been largely affected by decrease in mortality in infancy and childhood. However, there is no evidence at hand to indicate an increased expectation of life for adults or the aged.

A study of present-day charts of death rate reveals the fact that the improvement made in the reduction of the death rate from tuberculosis and pneumonia, for instance, is being counterbalanced by the increasing death rate from heart disease. Dublin clearly emphasized this observation.

In a consideration of the possibility of extending human life, Dublin, in 1922, constructed a hypothetical life table based on the life table for states which were in the registration area of the United States in 1910. He expressed the most favorable mortality rate that might be anticipated in view of knowledge and actual accomplishments at the time he was writing. According to his figures, the expectation of life at birth was approximately sixty-five years.

\* Submitted for publication January 16, 1931.

Therefore, if sixty-five years may be said to represent the optimal expectation of present-day life, and if heart disease is the leading cause of death today, it seems desirable to investigate the status of the heart in aged persons.

**The Present Study. Material.** In order to obtain cases in which special consideration was given to the cardiovascular system, the records of all patients who had undergone electrocardiographic examination at The Mayo Clinic, from August 1, 1914, to January 1, 1930, were considered, and from these, cases of aged persons were selected. In order to avoid approximating the average accepted expectation of life, sixty-five years, the low age limit for patients in this study was arbitrarily set at seventy-five years. The oldest patient was ninety-six years of age. Under these limitations 700 cases were available for study, representing an incidence of 1.1 per cent of persons who had undergone electrocardiographic examination.

It must be acknowledged that the results of critical analysis of this selected material are not entirely comparable to those that might be derived from a similar number of cases of patients of the same ages as those selected taken from the general population or from other limited fields of the general population. It must be assumed that the majority of aged patients who seek medical advice at a clinic which is more or less distant from their homes have ailments that may not exist to the same degree and extent among patients in other groups.

**Age.** Owing to the fact that this study represents patients in seventeen separate years of life, it seemed desirable to simplify the statistics by considering the ages in combined periods of two years.

Nearly half (47 per cent) of the cases occurred in the age group seventy-five and seventy-six years. (Table I.) A progressive diminution in incidence occurred as age increased, as would be anticipated. Only 4 cases (0.5 per cent) occurred in the oldest age group which was enlarged to include patients, ninety-one to ninety-six years of age. Six hundred four (86.3 per cent) of the cases occurred among patients who had not reached the eighty-first year of life.

TABLE I.—AGE INCIDENCE.

Age group, years.	Cases.	Per cent.
75 and 76 . . . . .	329	47.0
77 and 78 . . . . .	185	26.4
79 and 80 . . . . .	90	12.9
81 and 82 . . . . .	46	6.6
83 and 84 . . . . .	23	3.3
85 and 86 . . . . .	14	2.0
87 and 88 . . . . .	9	1.3
91 to 96 . . . . .	4	0.5
Total . . . . .	700	100.0

**Sex Incidence.** The incidence of males to females in this series was almost 5 to 1. There were 571 males (81.5 per cent) and 129

females (18.5 per cent). The consistent predominance of males in all age groups is evident in Table II.

TABLE II.—SEX INCIDENCE.

Age group, years.	Cases.	Males.		Females.	
		Number.	Per cent.	Number.	Per cent.
75 and 76 . . . .	329	259	78.7	70	21.3
77 and 78 . . . .	185	152	82.1	33	17.9
79 and 80 . . . .	90	76	85.5	14	14.5
81 and 82 . . . .	46	37	80.4	9	19.6
83 and 84 . . . .	23	22	95.6	1	4.4
85 and 86 . . . .	14	13	92.8	1	7.2
87 and 88 . . . .	9	8	88.8	1	11.2
91 to 96 . . . .	4	4	100.0		
Total . . . .	700	571	81.5	129	18.5

The marked disproportion in sex incidence in the series of 700, including those who had heart disease and those who had not, was due in large measure to the fact that 186 patients (26.5 per cent) came to the Clinic because of the disease which so often affects aged men, benign prostatic hypertrophy. Also, the well-recognized greater incidence of heart disease among males influenced the sex incidence to a considerable degree, in this series; the ratio of men to women who had heart disease was 5 to 1. This difference in incidence is probably somewhat greater than that which would occur in a random selection of patients of similar age groups.

*Blood Pressure.* The blood pressure of all patients in this series was investigated. In many cases the average of several readings was taken; in others the records represent only a single reading. Owing to the fact that some of the later age groups were small, the statistical error obviously was greater than that which would occur with larger groups of cases. The figures, however, give the general tendency of blood pressure in the aged, especially with reference to hypertension. Studies of blood pressure that would allow comparison between the sexes was not attempted owing to the relatively small number of women.

Alvarez and Stanley, in studying the blood pressure of 6000 prisoners, ranging in age from fifteen to eighty-four years, found that the modal or most typical pressure varied little from youth to old age. Their observations also indicated that the mean or arithmetic average pressure did not increase until after the fortieth year. Among the male prisoners the percentage with systolic pressures of more than 140 mm. of mercury, in the age group twenty to forty years, remained constant, suggesting that those persons who had hypertensive readings at the age of forty years had similar readings at the age of twenty years. A pressure of 115 mm. is just as normal, these authors stated, and a pressure of 140 mm. is just as abnormal, in an old man as in a young one. They also found that diastolic pressure tends to rise several years in advance of systolic pressure.

In studying the systolic blood pressures in young men, Diehl and Sutherland based their investigation on 5122 students who entered the University of Minnesota. They found systolic pressures of 140 mm. or more in 16.2 per cent of their group examined in 1922 and in 9 per cent of their groups examined in 1923 and in 1924. In the latter groups systolic readings of 160 mm. or more occurred in 0.5 per cent and of 170 mm. or more in 0.1 per cent. Believing that excitement and nervous influences might account for the discrepancy between the group examined in 1922 and those examined respectively in 1923 and 1924, 209 students of the 389 with systolic readings of 140 mm. or more were reexamined, and only 15 per cent of these proved to have persistent hypertension.

In the present group 521 aged patients (74.5 per cent) had systolic blood pressures of 140 mm. or more. (Table III.) This is opposed to the results in young and middle-aged persons. Of patients with systolic blood pressure of 140 mm. or more 492 (70.3 per cent) were in the first three age groups, that is, from the age of seventy-five to eighty years, inclusive. Only 68 patients (9.7 per cent) had systolic blood pressures of 200 mm. or more, and these, likewise, were chiefly in the first three age groups. The systolic blood pressures of 414 patients (59.1 per cent) were within the range of 130 to 180 mm.

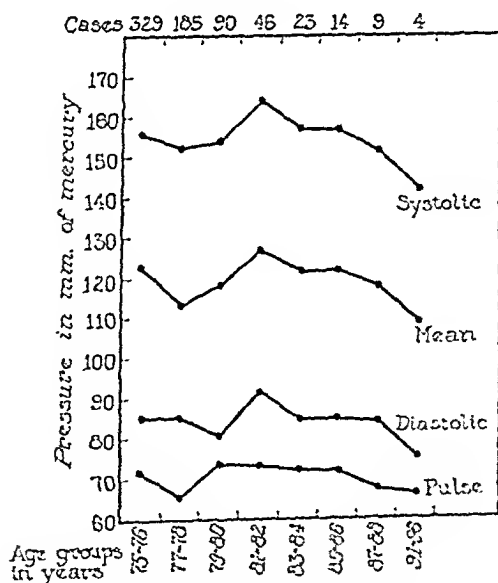


FIG. 1.—Average blood pressure and pulse readings.

The average systolic pressure according to age groups is shown in Fig. 1. These averages are not without considerable error owing to the great variation of the individual components of the various age groups. The average systolic reading in all age groups was

more than 140 mm.; the lowest average for any age group was 142.5 mm. The peak occurred in the age group eighty-one and eighty-two years in which the average systolic pressure was 164.2 mm.

The mean pressure or arithmetic average of the systolic and diastolic pressures (Tables III, IV and V) varied in a fairly parallel manner with the systolic pressure. (Fig. 1.) In a study of this type the mean pressure has little significance, owing to the fact that it is profoundly influenced by either abnormally high or abnormally low readings. The range of average mean pressures was 109 to 127.8 mm.

The diastolic blood pressure taken by itself did not parallel the systolic. Only 282 patients (40.3 per cent) had diastolic pressures of 90 mm. or more, which means that approximately one-third of the patients with systolic pressure greater than 140 mm. had normal or practically normal diastolic pressures. Only 75 patients (10.7 per cent) had diastolic pressures of 110 mm. or more. The diastolic blood pressure was between 60 and 120 mm. in the majority of cases; that is, in 464 (66.3 per cent). The averages of diastolic blood pressure, according to age groups, are shown in Fig. 1. With the exception of one age group, eighty-one and eighty-two years, the average diastolic pressures were less than 90 mm.

Pulse pressure was 60 mm. or more in 487 cases (69.6 per cent). (Table V.) Pulse pressures of 90 mm. or more occurred in 145 cases (20.7 per cent). The general trend of pulse pressure was in the range of 50 to 100 mm. where 504 cases (72 per cent) were placed. The averages of pulse pressure are shown in Fig. 1; all were in excess of 60 mm.; the highest average was 73 mm. and was recorded in the age group eighty-one and eighty-two years.

It is evident from the studies of blood pressure of the persons who comprised this aged group that hypertension is the rule; systolic blood pressures of 140 mm. or more occurred in 74.5 per cent, and diastolic blood pressures of 90 mm. or more occurred in 40.3 per cent of the cases.

Distinctly low blood pressure occurred infrequently; systolic blood pressure was less than 120 mm. in only 9.3 per cent and diastolic blood pressure less than 70 mm. in only 11 per cent of the cases.

*Patients Without Clinical Evidence of Heart Disease.* In a consideration of aged patients the failure to elicit symptoms and signs of heart disease does not by any means indicate that the heart is normal. The extremely high incidence of arteriosclerotic cardiovascular changes in senescence renders the possibility of finding a perfectly normal heart very remote. Robertson has stated that a normal heart is practically never observed at necropsy in a person who has passed the age of seventy-five years. Therefore, the group of patients under immediate consideration may be said merely not to have presented clinical evidence of heart disease. There were 315 patients (45 per cent) in this category. (Table VI.)



TABLE III.—SYSTOLIC BLOOD PRESSURE OF 700 PATIENTS SEVENTY-FIVE YEARS OF AGE AND OLDER.

Blood pressure, mm. of mercury.	Age group, years.												Total.				
	75 and 76.		77 and 78.		79 and 80.		81 and 82.		83 and 84.		85 and 86.		87 and 88.		91 to 96.		Per cent.
	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	
90 to 99	4	80.0	1	20.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0.7
100 to 109	14	66.6	3	14.3	4	19.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	3.0
110 to 119	20	51.3	7	17.9	5	12.8	3	7.7	2	5.1	1	2.6	1	2.6	0	0.0	5.6
120 to 129	24	40.0	18	30.0	11	18.3	6	10.0	0	0.0	1	1.7	0	0.0	0	0.0	8.6
130 to 139	28	51.8	13	24.1	6	11.1	3	5.5	0	0.0	1	1.9	2	3.7	1	1.9	7.7
140 to 149	48	46.2	25	24.0	16	15.4	4	3.8	9	5.8	3	2.9	0	0.0	2	1.9	14.9
150 to 159	35	41.2	26	30.6	11	12.9	6	7.1	1	1.2	2	2.3	3	3.5	1	1.2	12.1
160 to 169	38	37.4	37	36.4	13	12.7	2	1.9	8	7.8	2	1.9	2	1.9	0	0.0	14.6
170 to 179	43	62.3	14	20.3	6	8.7	5	7.3	0	0.0	1	1.4	0	0.0	0	0.0	9.9
180 to 189	23	39.7	20	34.5	3	5.2	6	10.3	6	10.3	0	0.0	0	0.0	0	0.0	8.3
190 to 199	16	45.7	8	22.9	6	17.1	4	11.4	0	0.0	1	2.9	0	0.0	0	0.0	5.0
200 to 209	15	71.4	4	19.0	1	4.8	0	0.0	0	0.0	0	0.0	1	4.8	0	0.0	3.0
210 to 219	9	33.3	2	13.3	3	20.0	4	26.7	0	0.0	0	0.0	0	0.0	0	0.0	2.1
220 to 229	9	53.0	3	17.6	3	17.6	1	5.9	0	0.0	1	5.9	0	0.0	0	0.0	2.4
230 to 239	4	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1.0
240 to 249	3	42.9	2	28.5	1	14.3	1	14.3	0	0.0	0	0.0	0	0.0	0	0.0	0.6
250 to 259	0	0.0	2	66.7	1	33.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0.4
260 to 269	0	0.0	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0.1
Total	329	.....	185	.....	90	.....	46	.....	23	.....	14	.....	9	.....	4	.....	100.0
Mean blood pressure	122.8	.....	114.0	.....	119.0	.....	127.8	.....	121.7	.....	121.7	.....	118.0	.....	109.0	.....	
Percentage over 140 mm.*	72.7	.....	77.3	.....	71.2	.....	74.0	.....	91.3	.....	78.6	.....	69.7	.....	75.0	.....	

\* Total number of patients with systolic pressure of 140 mm. and over, 521 (74.5 per cent.).

TABLE IV.—DIASTOLIC BLOOD PRESSURE OF 700 PATIENTS SEVENTY-FIVE YEARS OF AGE AND OLDER.

Blood pressure, mm. of mercury.	Age group, years.												Total.					
	75 and 76.		77 and 78.		79 and 80.		81 and 82.		83 and 84.		85 and 86.		87 and 88.		91 to 96.		Number.	Per cent.
	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.		
40 to 49	3	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	3	0.4
50 to 59	10	62.5	1	6.3	3	18.6	0	0.0	1	6.3	0	0.0	0	0.0	1	6.3	16	2.3
60 to 69	23	39.6	16	27.6	11	19.0	4	6.9	2	3.5	1	1.7	1	1.7	0	0.0	58	8.3
70 to 79	67	50.4	38	28.6	16	12.0	9	6.8	1	0.7	0	0.0	2	1.5	0	0.0	133	19.0
80 to 89	82	39.4	64	30.8	26	12.5	12	5.8	10	4.8	7	3.4	4	1.9	3	1.4	208	29.7
90 to 99	65	52.0	33	26.4	17	13.6	3	2.4	3	2.4	3	2.4	1	0.8	0	0.0	125	17.9
100 to 109	38	46.3	17	20.7	12	14.6	7	8.5	5	6.2	3	3.7	0	0.0	0	0.0	82	11.7
110 to 119	26	61.9	6	14.3	3	7.1	6	14.3	0	0.0	0	0.0	1	2.4	0	0.0	42	6.0
120 to 129	6	40.0	5	33.3	1	6.7	2	13.3	1	6.7	0	0.0	0	0.0	0	0.0	15	2.2
130 to 139	5	55.5	1	11.1	1	11.1	2	22.3	0	0.0	0	0.0	0	0.0	0	0.0	9	1.3
140 to 149	3	37.5	4	50.0	0	0.0	1	12.5	0	0.0	0	0.0	0	0.0	0	0.0	8	1.1
150 to 159	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1
Total	329	....	185	...	90	...	46	...	23	..	14	..	9	..	4	..	700	100.0
Mean blood pressure	122.8	....	114.0	...	119.0	...	127.8	...	121.7	..	121.7	..	118.0	..	109.0			
Percentage over 90 mm.*	43.8	....	35.7	...	37.8	...	45.7	...	39.2	..	42.9	..	22.3	..	0.0			

\* Total number of patients with diastolic pressure of 90 mm. and over, 282 (40.3 per cent).

TABLE V.—PULSE PRESSURE OF 700 PATIENTS SEVENTY-FIVE YEARS OF AGE AND OLDER.

Pressure, mm. of mercury.	Age group, years.														Total.		
	75 and 76.		77 and 78.		79 and 80.		81 and 82.		83 and 84.		85 and 86.		87 and 88.			91 to 96.	
	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.	Number.	Per cent.		Number.	Per cent.
20 to 29	8	80.0	1	10.0	0	0.0	0	0.0	1	10.0	0	0.0	0	0.0	0	0.0	
30 to 39	17	63.0	6	22.2	2	7.1	1	3.7	0	0.0	0	0.0	0	0.0	0	0.0	
40 to 49	34	41.7	18	23.8	14	18.1	7	9.2	0	0.0	2	2.6	1	1.3	0	0.0	
50 to 59	52	52.0	14	11.0	17	17.0	9	9.0	4	4.0	2	2.0	1	1.0	1	1.0	
60 to 69	47	35.6	47	35.6	16	12.1	8	6.1	7	5.3	4	3.1	2	1.5	1	0.7	
70 to 79	65	51.6	38	30.2	15	11.9	4	3.2	0	0.0	2	1.5	1	0.8	1	0.8	
80 to 89	39	46.4	24	28.6	8	9.5	3	3.6	7	8.3	0	0.0	2	2.4	1	1.2	
90 to 99	32	51.6	18	29.0	2	3.2	4	6.5	3	4.8	0	0.0	1	1.7	0	0.0	
100 to 109	12	35.3	1	32.4	6	17.6	4	11.8	1	2.9	0	0.0	0	0.0	0	0.0	
110 to 119	15	57.7	4	15.4	3	11.5	4	15.4	0	0.0	0	0.0	0	0.0	0	0.0	
120 to 129	3	25.0	1	8.3	5	41.7	2	16.7	0	0.0	0	0.0	0	0.0	0	0.0	
130 to 139	1	25.0	1	25.0	1	25.0	0	0.0	0	0.0	1	8.3	0	0.0	0	0.0	
140 to 149	2	40.0	2	40.0	1	20.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	
150 to 159	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	
160 to 169	1	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	
Total	329	....	185	....	90	....	46	....	23	....	14	....	9	..	4	..	
Mean blood pressure	122.8	....	114.0	....	119.0	....	127.8	....	121.7	....	121.7	....	118.0	..	109.0	..	
Percentage over 90 mm.*	66.3	....	79.0	....	63.4	....	63.1	....	78.3	....	71.5	....	66.7	..	25.0	..	

\* Total number of patients with pulse pressure of 60 mm. and over, 487 (69.6 per cent).

TABLE VI.—INCIDENCE OF HEART DISEASE IN VARIOUS AGE GROUPS AND IN ENTIRE GROUP.

Age group, years.	Cases.	Patients with evidence of heart disease.		Patients without evidence of heart disease.	
		Number.	Per cent.	Number.	Per cent.
75 and 76 . . . .	329	160	48.6	169	51.4
77 and 78 . . . .	185	89	48.1	96	51.9
79 and 80 . . . .	90	53	58.8	37	41.2
81 and 82 . . . .	46	38	82.6	8	17.4
83 and 84 . . . .	23	21	91.3	2	8.7
85 and 86 . . . .	14	13	92.8	1	7.2
87 and 88 . . . .	9	8	88.8	1	11.2
91 to 96 . . . .	4	3	75.0	1	25.0
Total . . . .	700	385	55.0	315	45.0

The sex incidence was the same as that in the entire series, namely, males, 262 (79.8 per cent), and females, 53 (20.2 per cent), or a ratio of 5 to 1.

In Table VII is found the diversified list of diagnoses made in this group of cases, and from this it is apparent that very few relatively normal old people were available for study.

TABLE VII.—CLINICAL DIAGNOSES IN CASES WITHOUT CLINICAL EVIDENCE OF HEART DISEASE.

Diagnosis.	Cases.	Diagnosis.	Cases.
Benign prostatic hypertrophy . . . .	136	Glaucoma . . . . .	2
Carcinoma . . . . .	48	Calculi in urinary bladder . . . .	2
Arteriosclerosis . . . . .	25	Uterine prolapse . . . . .	2
Chronic arthritis . . . . .	15	Chronic nephritis . . . . .	2
Peptic ulcer . . . . .	10	Pulmonary emphysema . . . . .	2
Chronic cholecystitis . . . . .	10	Exophthalmic goiter . . . . .	2
Negative examinations . . . . .	8	Constipation . . . . .	2
Adenomatous goiter with hyperthyroidism . . . . .	7	Thrombophlebitis of leg . . . . .	1
Diabetes mellitus . . . . .	7	Asthmatic bronchitis . . . . .	1
Hernia . . . . .	7	Esophageal diverticulum . . . . .	1
Pernicious anemia . . . . .	6	Syphilis . . . . .	1
Cataract . . . . .	4	Ulcer of urinary bladder . . . . .	1
Urethral stricture . . . . .	4	Neuritis . . . . .	1
Trifacial neuralgia . . . . .	3	Angioma . . . . .	1
Parkinson's disease . . . . .	2	Diverticulum of urinary bladder . .	1
		Lymphatic leukemia . . . . .	1

The electrocardiograms in this group did not reveal significant abnormalities. Premature contractions were found at the time of examination in 108 cases (34.3 per cent). They were of ventricular origin in 57 cases, of auricular origin in 32 cases and of nodal origin in 19 cases.

*Patients With Clinical Evidence of Heart Disease.* This group comprised 385 patients (Table VI), or 55 per cent of the entire series. The sex incidence was essentially the same as that in the entire group: males, 309 (80.3 per cent), and females, 76 (19.7 per cent), a ratio of 5 to 1.

The types of heart disease found in a group of aged patients are

very limited. Hypertensive or coronary disease comprised 381 (98.9 per cent) cases in the group studied.

In making clinical differentiation between cases of hypertensive heart disease and cases of coronary sclerosis I am mindful of the fact that these diseases coexist very commonly and, therefore, that the arbitrary division as given here is not without error. However, it was impossible accurately to select a group in which the two conditions were continued; therefore, the cases were classified according to the dominant clinical evidence, either as instances of hypertensive heart disease or of coronary disease. Further to emphasize the coexistence of these diseases, the records of necropsy at The Mayo Clinic disclose such coexistence in approximately 80 per cent of the cases in which either disease occurs.

Predominant hypertensive heart disease occurred in 209 cases, or 54.2 per cent. (Table VIII.)

TABLE VIII.—TYPES AND INCIDENCE OF HEART DISEASE.

Type of cardiac disease.	Age group, years.								Total.	
	75 and 76.	77 and 78.	79 and 80.	81 and 82.	83 and 84.	85 and 86.	87 and 88.	91 to 96.	No.	Per cent.
Hypertensive heart disease	92	44	28	23	12	7	3	0	209	54.2
Coronary sclerosis with angina pectoris	24	12	3	3	4	0	0	1	47	12.2
Coronary sclerosis without angina pectoris	44	31	20	12	4	6	5	2	124	32.2
Coronary thrombosis	0	0	1	0	0	0	0	0	1	0.3
Syphilitic aortitis	0	1	1	0	1	0	0	0	3	0.8
Chronic endocarditis with aortic insufficiency	0	1	0	0	0	0	0	0	1	0.3

Coronary disease occurred in 172 cases (44.7 per cent) and was represented by 47 cases with the anginal syndrome, 124 cases without painful seizures and only 1 case with coronary thrombosis. The extremely small incidence of coronary thrombosis (0.3 per cent) in this series of aged patients substantiates previous observations that its occurrence is most common between the fiftieth and the seventieth years of life. This may indicate that the majority of persons who attain advanced age are permitted to do so, in part at least, because they possess a sturdy and adequate coronary arterial tree, an endowment that is denied many other persons. This concept finds further support in the fact that, although the incidence of coronary sclerosis in this group was relatively high, acute occlusion was exceptional. This suggests that even in the presence of coronary disease cardiac nutrition is sufficient to permit life to be protracted definitely in excess of the accepted average.

The rarity of other forms of heart disease is evident; only 4 cases

(1.1 per cent) were recorded. There were 3 cases of syphilitic aortitis and 1 case of nonsyphilitic aortic insufficiency. It is not unlikely, of course, that in the analysis of a larger group of aged patients other forms of heart disease occasionally would be encountered.

Congestive heart failure at the time of examination occurred in 85 cases (22.1 per cent). More than half (54.1 per cent) of the patients who displayed this syndrome had dominant hypertensive heart disease.

The significant electrocardiographic abnormalities which occurred in cases of evident heart disease are shown in Table IX. *T* wave negativity occurred with greatest frequency; it was recorded in 96 cases (24.9 per cent). This abnormality occurred predominantly in Lead I; the incidence was 57 cases (14.8 per cent). It is interesting to observe that no instance of *T* wave negativity occurred after the eighty-fourth year; in other words, none in the oldest 27 patients of the entire group.

TABLE IX.—ELECTROCARDIOGRAPHIC CHANGES IN CASES OF EVIDENT HEART DISEASE.

Electrocardiographic changes.	Age group, years.								Total.		
	75 and 76.	77 and 78.	79 and 80.	81 and 82.	83 and 84.	85 and 86.	87 and 88.	91 to 96.	No.	Per cent.	Group, per cent.
<i>T</i> wave negativity in Lead I . . . . .	31	12	7	5	2	0	0	0	57	14.8	
<i>T</i> wave negativity in Leads I and II . . . . .	6	3	2	2	0	0	0	0	13	3.4	
<i>T</i> wave negativity in Leads II and III . . . . .	11	3	1	3	1	0	0	0	19	4.9	
<i>T</i> wave negativity in Leads I, II and III . . . . .	2	2	1	1	1	0	0	0	7	1.8	24.9
Complete block . . . . .	1	1	1	1	0	0	0	0	4	1.0	
Delayed auriculoventricular con- duction . . . . .	5	3	1	1	1	2	1	0	14	3.6	
Incomplete bundle-branch block . . . . .	4	4	3	2	0	0	2	1	16	4.2	
Complete bundle-branch block . . . . .	2	1	0	1	2	0	0	0	6	1.6	
Sino-auricular block . . . . .	1	0	0	0	0	0	0	0	1	0.3	10.7
Auricular fibrillation . . . . .	28	21	6	5	4	2	1	1	68	17.9	
Auricular flutter . . . . .	3	0	1	0	0	0	0	0	4	1.0	18.9

Disturbances in cardiac conduction were present in 41 cases (10.7 per cent). Incomplete bundle-branch block and delayed auriculoventricular conduction were most common and occurred in 16 cases (4.2 per cent) and 14 cases (3.6 per cent) respectively. The patients who exhibited delayed auriculoventricular conduction were all subjected to the atropin test, and the prolongation in transmission of impulse remained uninfluenced.

Among electrocardiographic abnormalities auricular fibrillation

occurred with greatest frequency. It was present in 68 cases (17.9 per cent). Auricular flutter was found in only 4 cases (1 per cent).

Premature contraction occurred in 123 cases (31.9 per cent), an incidence slightly more than that in the group of patients without clinical evidence of heart disease. They were of ventricular origin in 83 cases, of auricular origin in 19 cases and of nodal origin in 21 cases.

**Comment.** From this study of aged patients, one gleanes the impression that the majority of persons, even in the presence of evident heart disease, possess hearts of unusual quality. This impression becomes strengthened by the fact that only 85 patients (12.1 per cent of the complete series) had congestive heart failure. The heart, impaired or unimpaired by disease, that permits continuation of life to and beyond the seventy-fifth year is an organ of unusual quality.

**Summary.** This study is based on 700 patients seventy-five years of age and older who were carefully investigated with special reference to the cardiovascular system. The ages of the patients ranged from seventy-five to ninety-six years. Forty-seven per cent of the patients were aged seventy-five and seventy-six years. The numbers in the various age groups diminished progressively with advance in age; only 0.5 per cent were between the ages of ninety-one and ninety-six years. The ratio of the sexes was 5 men to 1 woman. Seventy and three-tenths per cent of the patients had systolic blood pressures of 140 mm. of mercury or more. Only 9.7 per cent had systolic blood pressures of 200 mm. or more. The mean blood pressure ranged from 109 to 127.8 mm. The diastolic blood pressure in 40.3 per cent of cases was 90 mm. or more. Diastolic pressures of 110 mm. or more occurred in 107 cases. Pulse pressures of 60 mm. or more occurred in 69.6 per cent of cases and readings of 90 mm. or more in 20.7 per cent. It is evident from this study that hypertension is the rule in aged patients. There were 315 patients (45 per cent) without clinical evidence of heart disease as opposed to 385 patients (55 per cent) with clinical evidence of heart disease.

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## THE TREATMENT OF THE GASTROCARDIAC SYNDROME (GASTRIC CARDIOPATHY).

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THE "gastrocardiac syndrome" is an expression which I coined, in 1912, in order to characterize certain hitherto little-known relations between stomach and heart, or, more generally speaking, between the digestive and circulatory systems. On the basis of extensive Roentgen ray studies I was able to demonstrate that many a so-called cardiac neurosis was, in reality, caused by some disturbance within the digestive tract. In fact, I am inclined to look upon the cardiovascular system as a sort of barometer which often registers organic or functional upheavals within the abdominal cavity and more particularly its upper left quadrant.

The "gastrocardiac syndrome," therefore, describes those disturbances of the circulatory system, and in particular the heart, which are produced by faulty function of the digestive tract, especially the stomach. Such disturbances may occur in patients both with normal or diseased hearts, and are due to one of two causes: (1) Mechanical: From dislocation of the heart and large vessels due to elevation of the left half of the diaphragm as a result of subdiaphragmatic accumulation of air, such as may be caused by various organic or functional anomalies. (2) Reflex: Through the effect of chemical and toxic substances within the stomach and intestines.

Of these two causes, the former is by far the more frequent. Whether the accumulation of air is within the stomach, the splenic flexure or generally distributed in the intestines, the diaphragm is almost always pushed upward more on the left side, because the weight of the liver restrains rightsided elevation. The heart, its free movements thus encroached upon, reacts, after a while, with disturbances of rhythm and causes definitely unpleasant sensations.

The reflex affection of the heart, which is often associated with the mechanical, is caused by a variety of ailments of the gastrointestinal tract. Among these, subacid or anacid conditions play a prominent rôle. Further, fermentation dyspepsia with marked flatulency, colitis localized in the transverse and descending colon, cholelithiasis, etc., are to be mentioned. On the other hand, ulcer or cancer of the stomach but rarely lead to cardiac disturbances.

It must, however, be admitted that not in every case does the heart become disturbed by leftsided elevation of the diaphragm. By distending the stomach with carbonic acid for experimental



studies, I found that certain individuals suffered no discomfort whatever, while others complained considerably of distress in the region of the heart. Yet, in both categories the heart itself was organically sound.

We may conclude from these experiments that the gastrocardiac syndrome can develop only if the heart responds too readily to stimuli. This may be the chief reason why we find such gastrocardiac symptoms primarily in people of middle or later life, and more particularly in patients of the wealthier classes who take but little exercise, eat too hastily and, in general, lead a life of high tension. In men dyspeptic heart symptoms occur most often in that time of life when the costal cartilages ossify and the thorax becomes rigid. Inasmuch as males are unaccustomed to costal breathing, interference with abdominal breathing such as would ensue from distention of the stomach or elevation of the diaphragm from any other cause is particularly unpleasant. Lack of habit and rigidity of the thorax render the costal type of breathing more difficult in males.

Patients with the gastrocardiac syndrome, as a rule, do not give the impression of being seriously ill. Yet they never feel quite well; they complain very frequently of distress in the left side which, usually, is diagnosed either as "nervous" or being due to some obscure heart lesion.

It is, of course, quite possible that occasionally such a patient may have a true heart disease, and in such a case the disordered stomach with its varying degrees of distention, the elevation of the diaphragm and the mechanical dislocation of the heart represent serious complications. In the majority of instances, however, one searches in vain for objective findings of cardiac affection in these patients.

Let us, then, first consider the gastrocardiac syndrome in a patient with a normal heart. The classical symptoms which, of course, need not be present in all cases with equal intensity are as follows: There is, particularly after meals, a dull and painful pressure at the left costal margin. This may take the form of anginoid distress, with pain radiating into the left arm. Pain behind the sternum is less often noticeable. Gas-producing foods, in particular carbohydrates and cellulose, seem to bring on these attacks rather readily, so that one may speak of certain idiosyncrasies. Then there is shortness of breath, an apparent inability of taking a deep breath. The abnormal distention of the stomach with air, which is often quite impressive on inspection, leads to irritation of the vagus nerve, and this again to bradycardia and extrasystole. Of this, the patient is acutely conscious, particularly if he is nervous or hears the action of his heart when lying on the left side. Or else, the irritation may give rise to tachycardia, to

vertigo and sensations of fainting, either because the cardia is kinked or the large vessels in the thorax are pressed upon; to a sense of fear or even of impending death, to syncope-like appearance, nausea, vomiting, hiccough, continued belching, etc.—in short, a complex of symptoms which at times may resemble Stokes-Adams syndrome and may assume alarming proportions, yet disappears as soon as the subdiaphragmatic air bubble has been removed by lavage of the stomach, an emetic or a purgative.

Objectively, the heart findings, as a rule, are normal if the patient has not eaten. At the height of digestion, however, the impulse of the apex is dislodged upward and outward. Percussion frequently yields loud tympanitic sound even above the left nipple, whereas there is dullness over the sternum and a relative dullness below the left clavicle. This latter phenomenon is due to the dislocation of the heart and a relative atelectasis of the upper left lung. The heart seems to lie transversely. On Roentgen ray examination it can clearly be seen how the excessive accumulation of air beneath the left diaphragm raises the apex of the heart and displaces the aorta in such a way that its ascending portion is curved toward the right side, a picture which closely resembles that of a sclerosis of the aorta. At times, however, with milder symptoms, the objective evidences of displacement are very difficult to detect.

Respiration is apt to be shallow and of the costal type. The patients complain of a multitude of dyspeptic symptoms and are discouraged because all previous medical attention has been unsuccessful. The conviction grows in them that the heart is at fault; for this reason they shun exercise, and this again leads to retention of even more gastrointestinal gas and to considerable increase in body weight, particularly if the patients, as is so often the case, are overeaters. Gradually the elevation of the diaphragm becomes more and more pronounced, and, as a direct consequence, the encroachment on the heart, the dyspnea, extrasystolia, pseudo-angina and other disagreeable sensations within the thoracic cavity are intensified. Since they know from experience that belching gives at least temporary relief, such patients try their best to eructate, and in doing so become in time more or less unconsciously air swallows. Thus a vicious circle is established which can be broken only if the attending physician is familiar with the true state of affairs.

The basis of successful therapy must needs be the discovery of the specific cause of the subphrenic air bubble and the removal of the accumulated gas. This latter procedure will, at the same time, do away with reflex and toxic sources of dyspeptic cardiac disturbances.

We know three causes of excessive accumulation of "gas" in the stomach or intestines, namely: (1) Aërophagy, that is, the invol-

untary swallowing of air, such as we find it in certain neurasthenics, in fast eaters, in overworked and worn-out people and as a voluntary habit in patients who have found relief from belching. (2) Insufficient absorption of gastric or intestinal gas and delay in their expulsion. This is due either to increased tonus of the vagus or to anatomic changes, such as pyloric stenosis, adhesions, kinks. (3) Increased formation of gas in the gastrointestinal canal, caused by abnormal fermentation and decomposition of unsuitable food in a gastrointestinal tract whose chemism is disturbed. Not infrequently several of these specific causes of air bubbles may be in combination.

Treatment must be applied: (1) To the psychic and general condition of the patient. (2) To the digestive apparatus (dietetic and medicinal therapy). (3) To the diaphragm (physiotherapy).

As has been mentioned before, two mistakes are very commonly made by physicians. These patients are either told that they are "merely nervous" and should pay no attention to their distress in the heart region; or their condition is diagnosed as a beginning arteriosclerosis and a carbohydrate diet supported by iodine and digitalis is prescribed. Obviously, both these modes of management are equally faulty and can only lead to an even firmer conviction of a serious heart trouble. It is, therefore, doubly important to quiet the patient's fears from the very beginning, to assure him that his heart is perfectly normal and that it is only his dyspepsia which needs attention. Since digestive disturbances are so much less alarming to the laity, his mind will be set at rest. In addition, his general condition must be improved. The obese—and these form the majority—must be reduced in weight and their musculature, including that of heart and diaphragm, be strengthened.

As to dietetic treatment, all gas-forming foods which contain much cellulose, cabbage, seed vegetables or legumes, fresh bread, particularly rye bread, raw fruit in large quantities must be excluded. Buttermilk and the like is preferable to sweet milk in acidity of the stomach. Carbonated waters are not to be advised. In general, the diet should be adapted to the personal experience of the patient and known idiosyncrasies should be taken into consideration. Overeating should at all times be avoided. Meals should be eaten slowly and the psychic side of the "pleasures of the table" emphasized. An occasional change from a vegetable-carbohydrate to a meat-fat diet sometimes yields astonishing results. In colitis the diet should be free from cellulose as far as possible, and combined with oil enemas. The meals should be small and well masticated. A mild form of exercise, such as a game of billiards or a short walk, is better than rest after eating, and abdominal massage, too, is of importance.

In the medicinal treatment of subacidity or acidity I have seen

excellent results from pepsin combined with hydrochloric acid in large doses; where the latter is not well borne citric acid is substituted. Hyperacidity requires atropin or any of the numerous antacids on the market. Belching may be promoted by the various derivatives of valerian (validol, bornyval, etc.). Not infrequently, a gastric lavage produces a magic effect, particularly in tachycardia and especially where the air bubble is caused by a chronic gastritis.

But nothing that is done with psychotherapy, diet or medicines is complete or promises to have a lasting effect unless it is supported by physiotherapeutic measures. The purpose of these is to accelerate venous circulation in the abdominal cavity and thereby reduce accumulation of gas, particularly beneath the left diaphragm. We, therefore, should resort to abdominal massage, gymnastics, "sitz-baths," halfbaths, nightly moist compresses, etc. Of equal importance is training in proper breathing technique. This means pre-eminently diaphragmatic breathing, which all patients with the gastrocardiac syndrome first have to practise in prone position and later keep up in sitting or standing posture. Diaphragmatic breathing is identical with the abdominal type of respiration: The hands bear gently down on the abdomen so as to provide a certain degree of resistance; the abdomen is slowly expanded as much as possible, without at the same time expanding the thorax, and kept in this position for a short time; it is then drawn inward to the greatest possible extent. This exercise not only affects the diaphragm, but also to a certain extent the heart and aorta, as one may observe on fluoroscopic examination. The musculature both of the diaphragm and the abdominal walls is gradually strengthened and its innervation led back to normal function. Simultaneously the liver is squeezed out like a sponge, whereby the entire circulation within the abdominal cavity is regulated and improved and the conditions for absorption of intestinal gases bettered. Later on systematic and graded mountain climbing, gymnastics, swimming, etc., is prescribed whereby the confidence of the patient is increased and the gaseous distention of the abdomen reduced.

Carried out in this systematic manner and for a sufficient length of time, this therapy of gastrocardiac symptoms in patients with sound hearts yields splendid results in the great majority of cases. The lowering of the left diaphragmatic dome can well be noted with the fluoroscope. In these cases the heart needs no special treatment; in fact, it might only do physical harm. Perhaps, too, the transition from a gastrocardiac neurosis to a real arteriosclerosis can thus be prevented.

Our problem is much more complicated if the described syndrome is found in patients with organic heart disease, in particular arteriosclerosis. The differential diagnosis between a pseudoangina due to abnormal elevation of the diaphragm and a beginning sclerosis

of the coronary arteries, with or without cardiac insufficiency, is at times extremely difficult and places the physician before a most responsible decision. The difficulty is even greater if the patient is an inveterate smoker with a nicotin angina and smoker's gastritis.

The final decision depends first on the functional test of the circulatory apparatus. Further, the effect of nitrites is of importance: nitroglycerin acts quite promptly in the earlier stages of coronary sclerosis, but as a rule, has no effect on the gastrocardiac symptoms of patients with normal hearts. Finally, this last class of patients are usually able to take a walk immediately after a hearty meal, while those with organic heart lesions, as a rule, cannot do so without marked distress, even if the coronary sclerosis is in its incipency.

As to treatment, the measures recommended for the purely functional gastrocardiac syndrome apply also to cardiac patients. In addition, each patient requires individualization as to exercise and rest, theobromin and other vasodilator remedies, nitrites, digitalis, balneotherapy, etc.

Psychically, it is wise to put the greater emphasis on the gastric and digestive disturbances when talking to such patients, so as to relieve their apprehension. As a matter of fact, the gastric treatment, the training of the diaphragm, the reduction of overweight, in short, the régime required in the treatment of the gastrocardiac neurosis, also exerts a favorable effect upon an organically affected heart because they reduce its load. Our therapy will be most successful if it takes into consideration not only the diseased organ, but also the interrelation between various organs. It is of such cases that Boadbent aptly says that "In practice the treatment of the stomach and nerves is more successful than treatment of the heart itself."

**Summary.** Attention is called to a group of cardiac symptoms which are produced by disturbances of the digestive tract, more particularly by an excessive accumulation of air in the stomach. This complex of symptoms for which the term "gastrocardiac syndrome" (gastric cardiopathy) is proposed, occurs most frequently in persons with a normal circulatory system. It is extremely annoying and often very alarming, and is apt to give rise to mistaken diagnoses of heart disease and inappropriate treatment. Organic cardiac lesions may, coincidentally, exist in patients with this gastrocardiac syndrome and complicate the latter condition considerably, but an exact differential diagnosis is not difficult. The proper treatment of gastric cardiopathy consists, in the main, of diet, certain drugs and physiotherapeutic procedures, and yields splendid results in the great majority of the cases.

## AN ANALYSIS OF ONE HUNDRED EXAMPLES OF CARDIAC PAIN IN PRIVATE PRACTICE.\*

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It is often supposed that the cardiologist has mainly to deal with chief complaints such as edema, dyspnea and palpitation. Such, however, is not the case. The most important chief complaint with which the cardiologist is concerned in private practice is cardiac pain. It seems that shortness of breath, as a rule the earliest manifestation of a gradually failing heart muscle, is not the complaint that brings the patient to him, but cardiac pain, Nature's other "danger signal," prompts the patient to seek medical advice.

This article summarizes the results obtained from a study in detail of 100 cases with a chief complaint of precordial pain. These patients were all ambulatory office patients, and only cases where cardiac pain was the primary complaint have been included. In this summary many of the details have been omitted and only a few of the most interesting results are presented. No attempt has been made to seek out any particular type of patient with a presenting symptom of cardiac pain. The patients were taken in consecutive order as the files of the office were consulted from February, 1927, to January, 1930. In order to obtain 100 cases with pain as a presenting symptom 401 cases had to be reviewed.

**Incidence and Arbitrary Grouping.** One is impressed by the high incidence of cardiac pain. Practically 25 per cent of all patients visiting our office have this as a primary complaint. Due consideration is taken, however, of the fact that we are dealing, for the most part, in our practice, with degenerative heart disease. To classify a group of people with this complaint immediately becomes very difficult, because it must be considered a symptom complex, and any arbitrary grouping will not be correct. For example, a case placed in the arteriosclerotic group may have suffered from a mild coronary episode, and the hypertensive may or may not have arteriosclerosis as an etiologic factor. Likewise, the patients grouped as angina pectoris with negative findings may be the victims of sclerotic changes in the coronary arteries. It is

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also possible that the coronary patient may well have been classified in the hypertensive group prior to occlusion. The following procedure has been adopted (Table 1a):

TABLE 1a.—INCIDENCE ACCORDING TO CLINICAL CLASSIFICATION.

Hypertensive	22
Arteriosclerotic	29
Syphilitic	2
Rheumatic	4
Thyroid	1
Coronary pathology	11
Angina pectoris	26
Obesity	1
Effort syndrome	4
Total	100

In the hypertensive group are placed patients whose records show no obvious coronary attack nor inordinate degree of arteriosclerosis upon examination of the peripheral vessels or of the eye grounds. A diastolic pressure of 100, or greater, has been used as an index.

The arteriosclerotic patients are usually of the sixth or seventh decade, with low blood pressure, where unmistakable coronary pathology could be excluded by history and whose symptoms were referable to a dying myocardium.

The rheumatic, syphilitic and thyroid classifications were made according to etiological evidence.

The patients in the angina pectoris group were between the ages of 35 and 55 years, the majority of whom showed negative findings in the physical examination, 2-meter Roentgen ray plate and electrocardiographic record. (The character and duration of the pain and absence of other symptoms were not characteristic of coronary disease.)

Patients have been selected for the coronary group according to a history of prolonged pain, abdominal symptoms, sweating and collapse, fever, leucocytosis and pericardial rub, or, in other words, the syndrome now recognized as coronary thrombosis.

The patient in the obesity group is believed to be suffering from endocrine dysfunction, and a favorable report has been received after pituitary therapy.

The effort-syndrome group includes 4 patients who show the usual manifestations of this condition, with cardiac pain as a prominent symptom.

*Family History.* Of the entire series 50 per cent gave a family history of cardiovascular disease, nephritis or diabetes. The hypertensive group showed a higher percentage of hereditary predisposition (Table 1b).

*Occupation.* Very rarely is a discussion of cardiac pain free from reference to incidence among physicians. Table 2 shows 5 per cent

of this class in the angina pectoris and coronary groups, and also gives confirmatory evidence of general knowledge of the high frequency of occurrence among brain workers. Due consideration, of course, must be given to the economic and social levels of an office clientele.

TABLE 1b.

	Cases.	Positive family history.	Percentage.
Hypertensive . . . . .	22	14	64
Arteriosclerotic . . . . .	29	13	45
Syphilitic . . . . .	2	1	50
Rheumatic . . . . .	4	2	50
Thyroid . . . . .	1	1	100
Coronary . . . . .	11	5	45
Angina pectoris . . . . .	26	13	50
Obesity . . . . .	1	1	100
Effort syndrome . . . . .	4	0	0
Total . . . . .	100	50	50

TABLE 2.

	Hypertensive.	Arteriosclerotic.	Syphilitic.	Rheumatic.	Thyroid.	Coronary.	Angina pectoris.	Obesity.	Effort syndrome
Physician . . . . .	3	1	..	..	..	2	3		
Housewife . . . . .	8	5	..	1	1	1	4		
Merchant . . . . .	3	4	1	..	..	1	4		
Manufacturing . . . . .	3	3	..	1	..	1	3		
None . . . . .	..	1	..	..	..	..	..	..	1
Publishing . . . . .	..	..	..	..	..	..	2		
Real estate . . . . .	..	2	..	..	..	..	..		
Clerk . . . . .	..	..	..	1	..	..	4	..	1
Artisan . . . . .	1	1	1	..	..	..	2	..	1
Clergyman . . . . .	..	..	..	..	..	1	..		
Accountant . . . . .	..	1	..	1	..	..	..		
Corporation executive . . . . .	..	2	..	..	..	1	..		
Retired . . . . .	2	2	..	..	..	..	1		
Lawyer . . . . .	1	3	..	..	..	1	..		
Domestic service . . . . .	..	2	..	..	..	..	..	1	
Teacher . . . . .	..	2	..	..	..	..	..		
Tailor . . . . .	..	..	..	..	..	1	..		
Broker . . . . .	..	..	..	..	..	..	1		
Dentist . . . . .	..	..	..	..	..	1	..		
Optometrist . . . . .	..	..	..	..	..	1	..		
Agent . . . . .	..	..	..	..	..	..	1		
Insurance . . . . .	..	..	..	..	..	..	1		
Oysterman . . . . .	1	..	..	..	..	..	..		

*Age and Sex.* No new facts have been determined in this part of the investigation. As one would expect, we find a slightly higher rate of occurrence among males in the hypertensive group; a higher percentage in the arteriosclerotic group; a striking predominance of the male sex in the coronary and angina pectoris divisions. We note the average age at the time of the first examination for the



hypertensive, arteriosclerotic and coronary groups, varying between 58.4 and 60.4 years, in contrast to the average of 48.8 years for the angina pectoris patients. (Table 3.)

TABLE 3.

	Male.	Female.	Average age at time of first examination.
Hypertensive . . . . .	12	10	60.4
Arteriosclerotic . . . . .	21	8	58.4
Syphilitic . . . . .	2	..	44.0
Rheumatic . . . . .	2	2	30.5
Thyroid . . . . .	..	1	47.0
Coronary . . . . .	10	1	59.7
Angina pectoris . . . . .	23	3	48.8
Obesity . . . . .	..	1	58.0
Effort syndrome . . . . .	3	1	33.5

**Analysis of Pain and Secondary Complaints.** We find exertion as an exciting cause occurring in numerical proportion in all groups. Dyspnea as a secondary symptom is noted only in 6 of the angina pectoris group. Four of the entire number of cases manifested apprehension—fear of impending death—and it is of interest to find 3 classed in the functional angina pectoris division and the remaining 1 as coronary. Three of the 4 rheumatic cases, all suffering with mitral disease, showed constant pain which we believe to be of fatigue origin. The absence of aortic-valve involvement in this very small group of cardiac rheumatics is contrary to general observation, and is considered worthy of mention. Over 50 per cent of the coronary group also suffered with constant pain. This high percentage is outstanding as compared with the other clinical varieties of degenerative heart disease. Vertigo as a secondary symptom more frequently complicated cardiac pain among the arteriosclerotics. (Table 4.)

TABLE 4.

	Character.					Exciting cause.			Secondary symptoms.			
	Constant.	Paroxysmal.	Dull pressure.	Stabbing, burning or choking.	Radiation to arms, jaw or shoulders.	Exertion.	Meals.	Exposure to cold or wind.	Dyspnea.	Vertigo.	Nausea or vomiting.	Apprehension.
Hypertensive . . . . .	5	16	2	1	12	15	1	..	8	1	2	
Arteriosclerotic . . . . .	2	22	7	5	13	19	4	12	9	4		
Syphilitic . . . . .	..	2	1									
Rheumatic . . . . .	3	1	..	2	1	2	..	..	2			
Thyroid . . . . .	1	..	..	1								
Coronary . . . . .	7	4	..	2	6	5	1	..	2	1	1	1
Angina pectoris . . . . .	3	17	3	4	8	12	..	2	6	1	3	3
Obesity . . . . .	1	..	1									
Effort syndrome . . . . .	2	2	..	1	..	2	..	..	..	1		

**Clinical Course of Groups.** This information was obtained from ordinary clinical observation in office practice and by means of replies obtained from a questionnaire sent to patient, friend, or physician. The hypertensive cases show the highest mortality with no patient symptom-free, and very few classed as improved. The arteriosclerotic has the lowest group mortality rate and a very satisfactory number classed as improved. While no coronary patient may be classed as symptom-free, the living patients could be grouped as unchanged or improved. Nearly 50 per cent of the total angina pectoris patients were improved, and in addition 4 reported as being symptom-free. (Table 5.)

TABLE 5.

	Died.	Group mortality, per cent.	Worse.	Unchanged.	Improved.	Symptom-free.	No information available.
Hypertensive . . . . .	9	41	2	3	5	..	3
Arteriosclerotic . . . . .	3	10	1	4	14	1	6
Syphilitic . . . . .	..	..	..	1	1	..	..
Rheumatic . . . . .	..	..	..	..	3	..	1
Thyroid . . . . .	..	..	..	..	1	..	..
Coronary . . . . .	4	36	..	3	4	..	..
Angina pectoris . . . . .	4	15	..	2	12	4	4
Obesity . . . . .	..	..	..	..	1	..	..
Effort syndrome . . . . .	..	..	1	1	1	..	1

**Electrocardiographic Study.** In reviewing the electrocardiographic findings several interesting features may be noted. Forty per cent of the angina pectoris group showed no abnormality. The 4 effort syndrome patients, as would be expected, gave evidence of somatic tremor, otherwise negative. Two of the 3 cases of auricular fibrillation are found in the rheumatic group. There was a relatively high incidence of ectopic ventricular contractions among the arteriosclerotic patients, these 29 patients presenting this disturbance in greater number than was observed among the remaining 71. More than 33 per cent of the coronary cases showed a negative *T* wave in the first lead. "Pardee's sign" (convex *S-T* interval) was found in one instance. Among the 11 no record in this group could be classified as "normal mechanism, no evidence of cardiac pathology." (Table 6.)

**Electrocardiographic Study of Fatal Cases.** In this analysis we observe serious changes in the graphic records of all groups, with the exception of the angina pectoris class, where 2 out of 4 patients showed no abnormality of a grave nature. Eleven out of 20 manifested depression or negativity of the Lead I *T* waves. Pardee's sign is noted as present in 1 of the arteriosclerotic groups. (Table 7.)

TABLE 6.—ELECTROCARDIOGRAPHIC FINDINGS.

	Hypertensive.	Arteriosclerotic.	Syphilitic.	Rheumatic.	Thyroid.	Coronary.	Angina pectoris.	Obesity.	Effort syndrome.
Left axis deviation . . . . .	13	20	..	1	..	6	8	1	
Right axis deviation . . . . .	1	..	..	1	..	..	..	..	..
Intraventricular block . . . . .	1	2	..	..	..	..	..	..	..
Right bundle-branch block . . . . .	1	2	1	..	..	..	..	..	..
Auricular fibrillation . . . . .	..	1	..	2	..	..	..	..	..
Ectopic auricular contractions . . . . .	2	2	..	..	..	2	..	..	..
Ectopic ventricular contractions . . . . .	1	6	..	..	..	2	1	..	..
Prolonged auriculoventricular conduction . . . . .	2	5	..	..	..	1	4	..	..
Sinoauricular block . . . . .	..	..	..	..	..	..	1	..	..
Sinus bradycardia . . . . .	..	..	..	..	..	..	1	..	..
Partial heart block (2:1) . . . . .	..	..	..	..	..	..	1	..	..
Negative <i>T</i> wave, Lead I . . . . .	4	4	..	..	..	3	..	..	..
Negative <i>T</i> wave, Leads I and II . . . . .	1	1	..	1	..	..	2	..	..
Negative <i>T</i> wave, Leads I, II and III . . . . .	..	1	..	..	..	..	..	..	..
Negative <i>T</i> wave, Leads II and III . . . . .	2	..	1	..	..	..	1	..	..
Depressed <i>T</i> wave, Leads I and II . . . . .	2	3	..	..	..	2	1	..	..
<i>Q-R-S</i> low voltage . . . . .	2	..	..	1	..	2	1	..	..
<i>Q-R-S</i> marked notching or slurring . . . . .	6	5	..	..	..	3	4	..	..
Prominent <i>Q</i> waves . . . . .	3	2	..	..	1	2	3	..	..
Convex <i>R-T</i> interval . . . . .	..	1	..	..	..	1	1	..	..
Negative findings . . . . .	1	1	..	1	..	..	10	..	4

TABLE 7.—RECORDS OF TWENTY FATAL CASES.

Records.	Clinical class.	Positive electrocardiographic findings.
IISF . . . .	Hypertensive	Left axis deviation; notched <i>Q-R-S</i> ; <i>T</i> , I and II diphasic.
IIPD . . . .	Hypertensive	Left axis deviation; <i>T</i> , I negative.
ISBD . . . .	Hypertensive	Left axis deviation; <i>T</i> , I and II negative.
IOFF . . . .	Hypertensive	Left axis deviation; <i>T</i> , I negative; deep <i>Q</i> , I.
IOSL . . . .	Hypertensive	Left axis deviation; aur.-vent. conduction (20); <i>Q</i> , I present.
IIIL . . . .	Hypertensive	Left axis deviation; <i>T</i> , I negative.
IHLF . . . .	Hypertensive	Right branch block.
IBFF . . . .	Hypertensive	Left axis deviation; aur.-vent. conduction (24); ectopic vent. beats.
IBOH . . . .	Hypertensive	<i>T</i> , I negative; <i>Q-R-S</i> , slurred; extremely low voltage.
IIPD . . . .	Angina pectoris	Left axis deviation; otherwise negative.
IHLL . . . .	Angina pectoris	Deep <i>Q</i> , II; otherwise negative.
ISFL . . . .	Angina pectoris	Prolonged aur.-vent. conduction (24); slurred <i>R</i> , II upstroke.
IBDII . . . .	Angina pectoris	Left axis deviation; <i>T</i> , I and II negative.
IHBL . . . .	Coronary	<i>T</i> , I negative; slurring of ventricular spikes.
IIHID . . . .	Coronary	<i>T</i> waves, isoelectric; slurring of ventricular spikes.
IHL D . . . .	Coronary	Left axis deviation; <i>Q-R-S</i> slurred; low-voltage; ectopic vent. beats.
IOFS . . . .	Coronary	Left axis deviation; <i>T</i> waves, isoelectric.
IBFF . . . .	Arteriosclerosis	Intraventricular block ( <i>Q-R-S</i> 14).
IBFP . . . .	Arteriosclerosis	Left axis deviation; auricular fibrillation; ectopic vent. beats.
IBIH . . . .	Arteriosclerosis	Left axis deviation; <i>T</i> , II and III negative; slurred, notched <i>Q-R-S</i> ; <i>S-T</i> , convex.

**Summary and Conclusions.** 1. The patient seeks advice of the cardiologist mainly on account of cardiac pain.

2. Over a 3-year period 401 cases occurring in office practice were reviewed, of whom 100 presented cardiac pain as the prominent symptom.

3. The patients were grouped arbitrarily as follows: hypertensive, arteriosclerotic, rheumatic, syphilitic, thyroid, angina pectoris, obesity, effort syndrome.

4. Exertion appeared most frequently as an exciting cause in all groups.

5. Highest mortality occurred in the hypertensive group and the lowest in the arteriosclerotic group.

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## RHEUMATIC FEVER IN ADULT PORTO RICAN IMMIGRANTS.

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THE different character and course of rheumatic infection in children and adults have been repeatedly emphasized in recent years. Ehrström<sup>1</sup> and Swift in particular have pointed out the analogy between tuberculosis and rheumatic fever: "the fact that in both tuberculosis and rheumatic fever severe general acute manifestations are more frequent in the young than in the old. In succeeding decades of life there is a transition from generalized manifestations to more localized lesions."<sup>2</sup> It is believed that this difference is determined by the development of an allergy to the infectious agent. This allergy in the adult may be brought about, not alone by earlier frank rheumatic infections, but very possibly by repeated exposures to the virus, which give rise to no clinical evidences of the disease. According to this view, the adult reacts differently than does the child to rheumatic infection because previous contact with the virus of the disease has altered his tissue and humoral reaction to its invasion. The ubiquity of rheumatic infection in temperate climates explains the typical adult reaction to rheumatic infection.

Many instances are on record of the increased invasiveness and the fulminating character of various infectious diseases striking for the first time a nonimmune adult population. The malignancy of measles affecting an isolated community of Samoan natives has often been cited.<sup>3</sup> The Senegalese when brought to France during the World War were affected in great numbers with an acute progressive form of generalized tuberculosis.<sup>4</sup>

Recently I observed what seems to be an analogue, a severe infection with rheumatic fever in a Porto Rican adult. The idea suggested itself that perhaps this increased virulence of the disease might be explained by the absence of rheumatic infection in Porto Rico, resulting in a greater susceptibility of Porto Ricans on exposure to the disease in the United States where rheumatic fever is endemic. This paper represents an attempt to test the validity of this assumption.

Accordingly all of the hospital records of the past three years of Porto Ricans with rheumatic fever or rheumatic heart disease, as well as 100 charts of the past three years, selected at random, of non-Porto Ricans who were treated for the same conditions were studied. Of the non-Porto Ricans, who for the sake of brevity will be referred to as "controls," 43 were American born and 51 were foreign born. Most of the foreign-born came from Russia and Central Europe where rheumatic fever is endemic. Included with the Porto Ricans are 3 from the British West Indies, 1 from the Virgin Islands, 1 from Venezuela, and 1 from South Carolina. Only patients fifteen years and older were included in the study.

TABLE I.—RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE IN PORTO RICANS AND CONTROLS.

	Controls.	Porto Ricans.
Number of cases:		
Males . . . . .	36	9
Females . . . . .	64	9
Total . . . . .	100	18
Average age, years . . . . .	32.0	26.6
Number of foreign born . . . . .	57	18
Average age on immigration . . . . .	21.0	19.8
Average age at first infection . . . . .	16.5	22.6
Patients admitted for rheumatic fever:		
Number . . . . .	35	13
Average age . . . . .	29.8	24.5
Patients admitted for cardiac insufficiency:		
Number . . . . .	43	2
Average age . . . . .	37.5	28.0
Patients admitted for miscellaneous conditions:		
Number . . . . .	22	3
Average age . . . . .	29.0	35.0
Number with cardiac lesions and no history of infection . . . . .	20	1
Number with history of chorea . . . . .	9	0

Tables I and II summarize the findings in the two series. The controls were on the average five years older than the Porto Ricans, and the foreign born among them, on their arrival in the United States, were on the average one year older than the Porto Ricans were at the time of their immigration. Striking is the fact that not one of the Porto Ricans gave a history of rheumatic infection before coming to this country. Their average age at the time of immigration was 19.8 years, while the average age on the occasion of the first rheumatic infection was 22.6 years. This contrasts

with an average age at the time of first infection of 16.5 years for the controls. Almost one-half of the foreign born controls had had their original infection in the country of their birth. A number of the Porto Ricans contracted their infection very soon after arriving in New York City. Only two of the Porto Ricans were admitted to the hospital because of cardiac failure, whereas nearly one-half of the controls sought treatment for cardiac insufficiency. Porto Rican immigration has been very active for only a few years, and since valvular disease develops only after their arrival in this country, the time has been too short for the evolution of advanced valvular lesions.

TABLE II.—CASES OF ACTIVE RHEUMATIC FEVER.

	Controls.	Porto Ricans.
Number of cases . . . . .	35	13
Average age, years . . . . .	29.8	24.5
Duration, weeks . . . . .	7.4	9.8
Number with pericarditis . . . . .	6	5
Number with violent onset . . . . .	1	6
Number with nodules . . . . .	1	1
Number in whom severity of disease was:		
Mild . . . . .	9	2
Moderate . . . . .	15	2
Severe . . . . .	11	9
Deaths . . . . .	5	3

Three quarters of the Porto Ricans were admitted to the hospital for some manifestation of acute rheumatic fever, whereas only one-third of the controls sought hospital care for this reason. The average age of these Porto Ricans was 24.5 years, and of the controls with acute febrile episodes 29.8 years. This difference of five years in the ages of the two series hardly seems great enough to account for differences in the severity of infection, yet for the most part, the disease was more acute, more prolonged, and more protean in its manifestations in the Porto Ricans. The severity of an infection by an unknown virus is difficult to judge objectively, but certain data are helpful. The duration of the bout of rheumatic fever for which the several patients were admitted was on the average 9.8 weeks in the Porto Ricans, and 7.4 weeks in the controls. Five, or 38 per cent of the Porto Ricans developed pericarditis, whereas only 6 or 17 per cent of the active cases of rheumatic fever among the controls had pericardial involvement. Six of the 13 Porto Ricans had a dramatic onset of the disease with chills, or with epigastric pain and vomiting; only two of the 25 controls, had such a stormy onset. It is interesting that none of the Porto Ricans had had chorea nor were seen with chorea, whereas 9 of the controls had histories of chorea. One adult Porto Rican and 1 control exhibited rheumatic nodules. Three Porto Ricans and 5 controls died from their infection.

An attempt was made to classify the severity of the infection in each case. Criteria were the violence of onset, the duration, the variety and extent of the clinical manifestations, and the gravity of the cardiac infection. Among the Porto Ricans 2 cases were mild, 2 were moderately severe and 9 were severe; among the controls 9 cases were mild, 15 were moderately severe, and 11 were severe, judged by these criteria. In both groups the average duration of the mild cases was four weeks, of the moderately severe cases seven weeks, and of the severe cases 11.7 weeks for the Porto Ricans and 9.6 for the controls. Neither the ages of the subjects nor the number of previous manifest rheumatic infections which they had experienced influenced the severity of the attacks. Indeed in the present control series the average age of the patients with the graver form of the disease was greater than that of those with the mild form.

Among North American and European patients with rheumatic heart disease one finds many who give no history of previous acute rheumatic episodes. These patients apparently have been subjected to a low grade chronic "subclinical" infection. Yet among the Porto Ricans of my series only one subject fell into this group and she had been in the United States for nine years when first observed. This is added evidence of the rarity of rheumatic fever in Porto Rico, and of the severity of the infection once it attacks a Porto Rican.

Twelve additional cases of rheumatic heart disease in Porto Ricans were found in the records of the cardiac clinic of the past three and a half years. Their average age was 24.4 years, their average age on immigration 18.5 years, and at the time of their first rheumatic infection 20.4 years. With one exception they were patients with early valvular lesions and no history of congestive heart failure. Seven of them exhibited only mitral insufficiency contracted after their arrival in the United States following mild attacks of fever and arthritis. Only one of this group had had a severe rheumatic infection. Two of the dispensary patients had definitely had rheumatic fever with cardiac involvement while in Porto Rico. One a girl, aged eighteen years, had had torticollis at the age of ten, and joint pains at the age of eighteen just before coming to the United States. Five months after her arrival she had mitral stenosis and insufficiency. The second patient, a man aged twenty years, had been ill with arthritis for six months at the age of fifteen while in Porto Rico. Two months after his arrival in the United States at the age of twenty the existence of a mitral stenosis was established. One Porto Rican girl of the dispensary group had chorea four years after coming to the United States.

The individual histories are more convincing than such statistical summaries on a small number of cases. The first case is the one that first drew my attention to the problem.

**Case Reports.** CASE I.—Hospital No. 316789, a Porto Rican male, aged twenty years, who came to New York City at the age of seventeen years, was admitted to Mt. Sinai Hospital on July 24, 1930. He had had no previous attacks of arthritis, tonsillitis or chorea. Five months before he had had sudden pain, redness and tenderness of both ankles and the right wrist. This lasted for four days. He then had a free interval of two or three days which was followed by a recurrence of the arthritis which again lasted a few days. Ever since then he has had repeated attacks of arthritis lasting a few days followed by a free interval of a few days. In these bouts the shoulder joints, the ankles, the tarsal joints, the knees, the wrists were successively or simultaneously involved. During the attacks he always had fever and at times true chills. Four days before admission there again was recurrence with fever and inflammation of the left knee, wrist, both ankles and the left shoulder. For three and a half months the patient had experienced dyspnea and palpitation on exertion, and in the outpatient department heart disease had been diagnosed.

Examination on admission revealed an acutely ill patient, with a temperature of  $104^{\circ}$ , a pulse of 112 and painful inflammation of both shoulders, the left sternoclavicular joint, the left wrist, both knees and ankles and the small joints of the left hand and of the feet. The heart was somewhat enlarged to the left and right. Presystolic and systolic murmurs were heard at the apex and a diastolic murmur along the left sternal margin. The white cell count totalled 17,500 with 77 per cent polymorphonuclears and 23 per cent mononuclears. The hemoglobin was 76 per cent. On the third day, as a result of active salicylate therapy, the temperature was normal and the joint inflammation had subsided. Coupled premature beats were heard. On August 4 the knuckles of the left hand and the knees were again painful; the heart rate was 108. On August 7 the hemoglobin was 75 per cent. On August 8 when the administration of salicylates had been stopped there again was pain in the left shoulder and the temperature rose to  $100^{\circ}$ . On August 18 he had been afebrile for one week. On the following day the proximal interphalangeal joint of the left index finger became swollen and painful, but subsided in a few days. The temperature during the first week ranged from  $98^{\circ}$  to  $104.4^{\circ}$ , during the second from  $98.6^{\circ}$  to  $100^{\circ}$ , the third from  $98.6^{\circ}$  to  $101.2^{\circ}$  and during the fourth was normal. Although the boy was soon afterward discharged, it is doubtful whether he was rid of his infection. Electrocardiograms during the course of infection showed prolongation of the *P-R* interval to 0.33 second and changes in the *S-T* segment.

*Summary.* A patient with a continuous infection for over six months, with repeated bouts of arthritis involving at various times a great number of joints, including many of the small joints. On admission there was a high leukocytosis. An active myocarditis was evidenced by electrocardiographic changes and a persistently rapid heart rate.

CASE II.—Hospital No. 311954, a Porto Rican, male, aged twenty-six years, was admitted to the hospital on March 5, 1930. He had had no attacks of arthritis, chorea or sore throat while in Porto Rico. He came to the United States at the age of twenty-three years. At the age of twenty-four years he had pain and swelling of both ankles, which lasted two months. Three weeks before his admission he became febrile and experienced severe pain and swelling of both knees. This was followed by pain in the toes, fingers and the left shoulder. On admission he appeared acutely ill, with severe pain and acute arthritis in the left knee and in the toes of the right foot and the interphalangeal joints of the right hand. The heart was slightly enlarged to the right. A short soft apical systolic murmur and a faint diastolic murmur to the left of the sternum were



audible. The white blood cells totalled 12,300, with 62 per cent polymorphonuclear cells. The hemoglobin was 92 per cent. The temperature during the first week ranged from  $101^{\circ}$  to  $104^{\circ}$ , during the second and third from  $99^{\circ}$  to  $101.5^{\circ}$ , the fourth from  $98.6^{\circ}$  to  $101^{\circ}$  and after this was normal. A few days after admission both knees and the left shoulder were involved. The following day a pericardial friction rub became audible. Then the right wrist became inflamed, a week later the left metacarpophalangeal joints, the next day both wrists. The pericarditis persisted, and on March 27 underwent an acute exacerbation. Electrocardiograms, taken at intervals during the infection showed on March 17 abnormal *R-T* transitions in Leads I and II, and on several occasions inverted *T* waves in Leads II and III. On April 4 the temperature finally became normal and the symptoms subsided. The patient was seen again on May 26, some weeks after his discharge from the hospital. By this time he had developed auricular fibrillation, although his valvular defects were not far advanced.

*Summary.* A young man with acute arthritis, pancarditis, and a febrile course of seven weeks, who during convalescence developed auricular fibrillation.

CASE III.—Hospital No. 302133, a negress from the British West Indies, aged twenty-nine years, who had come to the United States at the age of eighteen years. During her twenty-sixth year she was ill for the whole year with joint pains. Then a tonsillectomy was performed. Before this she had had frequent sore throats. She was admitted to the hospital on May 4, 1929, at the age of twenty-nine years. Two weeks previously she had had a chill which was followed by a sore throat and pains in all the joints, with swelling of the fingers of both hands. The pains gradually subsided but the fever continued. For three days preceding her admission she had had sticking pains in the left chest anteriorly and profuse sweats. Examination revealed an acutely ill woman. There was no swelling of any joints, but the elbows were painful on motion. The heart was enlarged to the left and right and a presystolic thrill and murmur were present at the apex. The pulmonic second sound was accentuated. The hemoglobin was 60 per cent; the white cells totalled 15,300, with 82 per cent polymorphonuclears and 18 per cent mononuclears. On May 11 acute pericarditis developed; on May 18 there was pain in the left knee. On May 31 the white cell count was still high—11,900, with 64 per cent polymorphonuclears, 34 per cent mononuclears and 2 per cent eosinophils. On June 12 the hemoglobin was 50 per cent. On June 21 a newly developed aortic diastolic murmur became audible. On June 30 many subcutaneous nodules appeared on the scalp, the elbows and the knees. By July 17 she was much better and was allowed out of bed. A few days later, however, there was a new rise in temperature and a fresh crop of rheumatic nodules appeared. During her whole stay in the hospital for twelve weeks her temperature ranged from  $99^{\circ}$  to  $103.2^{\circ}$ . It never remained normal more than a day or two, and was still elevated when she insisted upon leaving. On several occasions electrocardiograms showed prolongation of the *P-R* interval to 0.22 and 0.24 second, the last time just before her discharge, fourteen weeks after the onset of her illness.

*Summary.* A woman, the onset of whose illness was marked by a chill and sore throat, which was followed by arthritis and pericarditis and aortic valvulitis. Ten weeks later a crop of subcutaneous nodules appeared and after three more weeks a second crop. The fever lasted fourteen weeks and had not returned to normal when the patient escaped from observation.

Rheumatic fever is primarily a disease of the temperate zone. In the tropics it is much less common.<sup>5,6,7</sup> Indeed, in the southern United States the incidence of rheumatic fever is very low and it becomes rarer the further south one goes.<sup>8,9</sup> Dr. Pedro N. Ortiz, Commissioner of Health of Porto Rico, kindly supplied me with the following data on the crude death rate from rheumatic fever in Porto Rico.

DEATHS AND DEATH RATES PER 100,000 POPULATION, FROM RHEUMATIC FEVER  
IN PORTO RICO.

Fiscal year.	Deaths.	Death rates.
1925 to 1926 . . . . .	13	0.9
1926 to 1927 . . . . .	19	1.0
1927 to 1928 . . . . .	11	0.7
1928 to 1929 . . . . .	22	1.0
1929 to 1930 . . . . .	14	0.9

This compares with a crude death rate of 3 per 100,000 for the United States Registration area. Of the 22 deaths recorded for the year 1928-1929, 14 occurred in coastal towns, and 8 in the mountains of the interior.<sup>10</sup> Coburn<sup>11</sup> has gathered data showing that rheumatic fever is very rare in Porto Rico, but that occasional cases are encountered. Among 225 consecutive necropsies at the school of Tropical Medicine at San Juan no cases of acute or chronic rheumatic lesions of the heart were encountered.<sup>12</sup> In New York City and Boston the lesions of mitral stenosis are found in about 4 per cent of all necropsies. In New Orleans, however, the incidence is only 0.23 per cent.<sup>7</sup> These figures suggest that very possibly many of the deaths in Porto Rico attributed to acute rheumatic fever were due not to this disease but to some other condition. The classification of deaths as directly due to rheumatic fever is notoriously difficult and uncertain.

A somewhat conflicting statement appears in the report of the Surgeon General of the United States Army.<sup>13</sup> The annual admission rate per 1000 officers and enlisted men, for rheumatic fever among Porto Rican soldiers stationed in Porto Rico was 0.91 in 1926, and 1.63 in 1927, whereas the admission rate for white soldiers stationed in the United States was 0.65 in 1926 and 0.69 in 1927.

Of the 30 Porto Ricans with rheumatic fever and rheumatic heart disease whose records I have studied 2 gave histories of rheumatic infections before reaching the United States.

There are indications that negroes from the southern United States, who migrate to the North, react to rheumatic fever in much the same manner as do Porto Ricans. I have observed a case of severe rheumatic fever in a young negress from South Carolina, contracted shortly after her arrival in New York. Dr. John R. Paul informs me that from his studies in Philadelphia he has gained the impres-

sion that rheumatic fever in negroes recently arrived from the south runs an unusually severe course.

The data show clearly that rheumatic fever is rare in Porto Rico, and that the Porto Ricans who were observed while at Mt. Sinai Hospital contracted their infection after their arrival in the United States. This accounts for their more advanced age (22.6 years) at the time of their first infection.

Two further propositions are more difficult of proof: does rheumatic fever run a more severe course in Porto Rican immigrants; is this severer infection due to a greater susceptibility owing to lack of previous exposure in their native country?

Of course many individual cases of rheumatic fever of great severity are seen in adult native Americans. The distinguishing feature is that such cases among the native American population are the exception, among the Porto Ricans they are the rule. It is significant that, in 9 of the 13 Porto Ricans the disease was severe, that in the whole group the average duration of the febrile period was longer, and the incidence of pericarditis and the frequency of a stormy onset greater.

To explain why rheumatic fever in Porto Rican immigrants takes on a more fulminating form, certain analogies to the behavior of other infectious diseases attacking a nonimmune population have been pointed out. The thought will at once arise, why, if Porto Ricans lack immunity, do so few of them contract rheumatic fever when they come to the United States? One might imagine that the disease might assume true epidemic proportions among them. As a matter of fact the evidence that I have been able to gather suggests that rheumatic fever is uncommon among Porto Ricans in New York City. Mt. Sinai Hospital, because of its location near a large Porto Rican settlement attracts large numbers of Porto Rican patients, yet the number of rheumatics is few. The hospital statistics are confirmed by those of the dispensary. In the cardiac clinic from January 1, 1927, to September 1, 1930, only 33 Porto Ricans were admitted out of a total number of 936 new patients. Of these only 16 had rheumatic heart disease. The tuberculosis clinic of the hospital, on the other hand, reports that almost one-half of its patients are Porto Ricans.

Diseases vary in their degree of contagiousness, some such as measles attack practically every exposed nonimmune, others, and with these one must group rheumatic fever, are more highly selective in their distribution. The epidemics of rheumatic fever that have been described are characterized by a very slow diffusion of the contagion, and a rather limited extent.<sup>7,14</sup> It may be that massive doses of the virus are necessary for infection to take place. An analogy is offered by the course of development of tuberculosis in Senegalese troupes in France, already quoted. Only a fraction

of the soldiers contracted tuberculosis, but those who became infected had a very severe form of the disease. The nature of rheumatic fever is apparently such that it never gives rise to explosive, widespread outbreaks. A second factor limiting the spread of the disease may be the fact that the Porto Ricans in New York live a rather segregated life and do not mingle much with other peoples.

It is not climate alone that determines the varying susceptibility of different peoples to rheumatic infection. It has been shown that the morbidity from rheumatic fever in the same locality varies with the different races. Thus the French experience with their troops in Morocco is shown in the following table taken from Andrieu:

MORBIDITY OF ARTICULAR RHEUMATISM PER 1000.

	Years.					
	1908.	1909.	1910.	1911.	1912.	1913.
Senegalese . . .	5.20	17.98	18.71	16.29	14.47	8.23
Europeans . . .	15.96	11.40	6.44	15.15	11.05	6.44
Indigenous Arabs .	8.41	4.73	2.30	3.19	3.37	2.95

The Porto Ricans in New York, as well as in their native island, are very poor, and their living conditions are for the most part indescribably bad. Most of them have intestinal parasites, and syphilis is very prevalent among them. It is possible that these factors serve to aggravate the severity of rheumatic infection when it occurs.

In some equatorial regions rheumatic fever is quite common. Thus together with its cardiac sequelæ it is prevalent in Cameroon and in Togo, yet in East Africa it is rare. It is frequent in the West Caroline Islands and in the Marshall Islands and in Tahiti, yet in Samoa it is almost unknown.<sup>15</sup>

Certain other diseases exhibit incomprehensible vagaries in the tropics. Scarlet fever is so rare in the tropics that one might imagine that the indigenous population, lacking acquired immunity, would be peculiarly susceptible to it. Yet, whenever it has been introduced in far southern latitudes only local small epidemics have resulted.<sup>16</sup> Studies by Otero<sup>17</sup> have shown that in Porto Rico the hemolytic streptococcus is encountered in cultures of normal throats far less frequently than in New York City. Both he and Pomales<sup>18</sup> found the same basal throat flora as in the United States, namely, Gram-negative cocci and nonhemolytic streptococci. Sore throats and tonsillitis are common among Porto Ricans on their native island. Pomales found hemolytic streptococci in 32 per cent of 50 Porto Ricans with acute tonsillitis, and hemolytic staphylococci in many. Yet, sore throats in Porto Rico are rarely followed by rheumatic fever. This is additional evidence that the relationship of tonsillar infection to rheumatic fever is not so close as has been supposed.

**Summary.** Rheumatic fever and rheumatic heart disease are very rare in Porto Rico. Rheumatic infection is not very common among Porto Ricans who have immigrated to New York City, but when infection does occur it is apt to be severe and in adults tends to approach the childhood type of the disease. This occurred in 9 of 13 cases of active rheumatic fever studied at Mt. Sinai Hospital. The cause of the varying incidence and severity of rheumatic fever in Porto Ricans and inhabitants of the temperate zone remains obscure. The data thus far available point to the desirability of a more intensive study of the semeiology of rheumatic fever, with particular reference to the prevalence of the disease, not alone in Porto Ricans, but in all parts of the world. At the same time a correlated study of the character and incidence of throat infections should be made. Such investigations might lead to a better understanding of the climatic factors as well as of the immune processes of the disease.

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## THE CASE FOR AND AGAINST THE OPERATIVE TREATMENT OF ANGINA PECTORIS.

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ALL agree that the surgical treatment of angina pectoris is palliative only. Relief of pain, however, is always important, not only from the standpoint of the suffering of the patient, but also because, as suggested by Wenckebach and Daniélopou, the pain in itself may actually be injurious to the organism. It is apparently the consensus of opinion at present that operation for angina pectoris should be reserved for the more severe cases. Of our cases of angina pectoris we deemed only one severe enough to warrant the use of surgical procedures. Our experience, however, with this case was so unique that we were stimulated to study the subject of the operative treatment of angina pectoris more carefully. The following is a brief report of our case.

**Case Report.**—The patient, an asbestos worker, aged fifty-five years, entered Georgetown University Hospital on May 23, 1929, giving a history of attacks of pain in the precordia over a period of two and a half months. At first the attacks had occurred only after exertion, but had become more frequent and more severe and finally began to appear when the patient was sitting quietly. During the preceding week they had been much more intense at night than in the day. The patient stated that the attacks lasted from one-half to one hour and that during them "the heart felt as if it was being torn out of the chest." The pain passed across the chest, down into the abdomen, up into the neck and down the left arm. For about a year there had been mild dyspnea on exertion.

Physical examination was essentially negative. A third heart sound was heard and seemed to be presystolic in time. The blood pressure was 98 systolic and 62 diastolic. The pulse rate varied from 80 to 100. A roentgenogram of the chest revealed nothing abnormal. The urinalysis was essentially negative. The hemoglobin was 62 per cent (Dare), the erythrocytes numbered 3,160,000 per c.mm. and the leukocytes 7900, of which 81 per cent were polymorphonuclear neutrophils. The Wassermann and Kahn tests of the blood were negative. The electrocardiogram showed regular rhythm, rate 100, sinus tachycardia, conduction time 0.2 sec. The only change in the electrocardiogram was the gradual development of left axis deviation as time went on.

During ten days in hospital the pain was relieved promptly but only for a short time by tablets of  $\frac{1}{100}$  grain of nitroglycerin under the tongue. Ten to fifteen of these were required nightly but even then the patient had little rest.

On June 15 novocain with alcohol was injected into the first six left thoracic nerves paravertebrally by Dr. John Shugrue. On this day he had

one severe attack of pain but during the following three days was completely relieved. After this, however, the pain recurred and was as bad as before. In addition there were now some painful paresthesias over the left chest and inner side of the left arm.

On July 8, the left superior cervical sympathetic ganglion was removed by Dr. Shugrue under nitrous oxid, oxygen and ether anesthesia. During the next two weeks of convalescence in hospital there was almost complete freedom from pain. Soon, however, the patient began to complain of some pain in the left mandible and discomfort in the left axilla.

Shortly after leaving the hospital he began to experience great pain in the left jaw upon chewing, so much so that eating was an agonizing process, and his nutrition suffered accordingly. There were occasional attacks of precordial oppression, but no real pain.

In September the patient began also to complain of pain in the shoulders, especially the right. This pain gradually became more severe until it was present almost constantly and was excruciating. The muscles of both arms, especially the right, became markedly atrophic, and there was great limitation of motion at the right shoulder joint and some of the left. Roentgenograms revealed no abnormality of the shoulder joints, but the bones showed rarefaction. A careful neurologic examination was negative, except for Horner's syndrome on the left. It was thought that the patient might have a periartthritis of the shoulder joints with atrophy of disuse, and diathermy treatment was instituted. The possibility of transferred anginal pain was also considered. The pain in the jaw was attributed to a possible glossopharyngeal nerve involvement in the operative scar in the left side of the neck. The pain in the shoulders finally became so severe that there was no relief unless the patient was completely under the influence of morphin.

Two days before death he began to complain of dyspnea and showed slight pretibial edema. While pouring himself a cup of tea at supper time he suddenly died, November 25, 1929, eight and a half months after the onset of angina and four and a half months after the ganglionectomy.

Necropsy did not reveal any pathologic condition of the upper extremities. The arms were freely movable. There was bilateral hydrothorax. The heart weighed 455 gm. The coronary arteries were markedly sclerosed. The descending branch of the left coronary artery was apparently completely occluded by calcification, especially a short distance from its origin. There was some dilatation of the left ventricle, the apex of which was thin and bulging due probably to an old infarct. Evidence of fresh infarction was not found. There was moderate fibrosis of the myocardium.

In this case the patient would probably have been better off without his operation. His pain afterward was more severe, practically continual, more diffuse and the cause of great malnutrition. Pain in the jaw and face not infrequently follows this type of operation, and pains and annoying paresthesias of the chest and upper extremities are not uncommon. Naturally, if our treatment, which is aimed at relief of pain, itself is followed by other pain which may be just as severe, it is time to scrutinize that type of treatment to determine whether it is really worth while or whether it may not be improved upon.

We have collected and analyzed 138 cases of neurectomy for angina pectoris reported by forty-four various authors. (See Bibliography.) This is not a complete collection of recorded cases,

but we felt it to be sufficiently representative for our purpose. Before discussing this series of cases it would be well to make an inventory of our knowledge of the anatomy and physiology of the innervation of the heart and aorta and to discuss the nature of angina pectoris.

A summary of our knowledge concerning the innervation of the heart and aorta has been well given by Kuntz. A perusal of this shows how much there is yet to be learned on the subject. All of the nerves of the heart pass through the cardiac plexus which is situated at the base of the heart. These nerves are all sympathetic and vagal. The sympathetic nerves pass to and from the heart through synapses, mainly in the three cervical sympathetic ganglia, but also in the upper four or five thoracic ganglia. They are all apparently derived from the upper four or five thoracic spinal nerves. The efferent fibers accelerate and otherwise modify the heart beats doubtlessly by direct action upon the heart muscle. The afferent fibers (which pass through all of the sympathetic ganglia except the superior cervical) convey sensation, but also play some part in reflex vasomotor control. The vagal supply for the heart usually consists of three rami on each side. The fibers make synaptic connections in the cardiac plexus and also in ganglia in the heart itself. The efferent fibers are mainly inhibitory and exert their effect largely upon the sinoatrial node and the atrio-ventricular bundle. The afferent vagal impulses probably do not reach the threshold of consciousness, but elicit reflex vasomotor responses. The coronary arteries are supplied by both sympathetic and vagal fibers. The so-called depressor nerve is commonly regarded as a branch of the vagus, consisting mainly of afferent components which originate in the proximal parts of the aorta and adjacent cardiac wall. They exert their effect mainly upon the vasomotor and cardioinhibitory centers. This nerve is supposedly formed by a branch of the main trunk of the vagus which joins a branch of the superior laryngeal nerve. Surgeons apparently are not often certain of the location of this nerve.

Of all the theories of angina pectoris, that championed by Daniélopou appeals to us as being most plausible. In brief, this theory is based upon the assumption of an inadequate coronary circulation, whether there is coronary sclerosis or an apparently normal heart. Angina pectoris is much more frequent when the coronary arteries are severely sclerosed than when they are healthy. The anginal attack arises from a disturbance of the balance between the work of the myocardium and its blood supply. Looked upon in this way, the theory can account for the occurrence of angina attacks in perfectly healthy young adults, since even healthy coronaries may be faced by an excessive demand. The theory also explains the many cases of coronary disease without anginal symptoms; in these it may be assumed that the occlusion has occurred



so slowly that sufficient anastomosis has had time to develop to maintain the balance. In the angina due to syphilitic aortitis partial and sometimes complete occlusion of the orifices of the coronary arteries in the root of the aorta is responsible for the condition. The objections to this theory, we believe, are less serious than to the aortic hypothesis put forward by Allbutt, Wenckebach and others. The hypothesis of spasm of the coronary arteries we hold to be untenable.

It must be emphasized, however, that there are other cardiac pains than those of true angina pectoris, particularly those accompanying acute aortitis and those associated with a failing heart. The subject of this paper is strictly limited to true angina pectoris as first described so accurately by Heberden. We are assuming that the cause of the pain arises in the heart, affects the afferent fibers of the sympathetic system concerned with sensation and is reflected as pain felt in the area of distribution of the peripheral nerves of the same segments as those from which the sympathetic nerves originate.

Franck (1899) was the first to suggest cervical sympathectomy for angina pectoris. Although the operation was done several times for various conditions, it was not until 1916 that Jonnesco performed the operation first for angina pectoris. C. H. Mayo has stated that he performed bilateral cervical sympathectomy for angina pectoris in 1913, but he has never published this report. Since 1916 many surgeons have recorded a few of these operations. Probably several hundred have been performed. The greatest activity in this direction seems to have occurred from 1923 to 1928. Recently one hears rather little of sympathectomy in connection with angina pectoris. Latterly, the alcoholic injection of the upper dorsal nerve roots has been advocated, of which more will be said later.

Various types of operations have been performed in the neck, with some success from each. The most complete type is that of Jonnesco, who resected the sympathetic chain with the superior, middle and inferior cervical ganglia and the first thoracic or stellate ganglion. Of the 138 case reports analyzed by us the types of operation were as follows:

1. Jonnesco type, unilateral, 21 cases (19 on left alone, 2 on right alone).
2. Jonnesco type, bilateral, 4 cases.
3. Removal of left superior cervical ganglion, 21 cases.
4. Removal of right superior cervical ganglion, 2 cases.
5. Removal of both superior cervical ganglia, 2 cases.
6. Division of sympathetic trunk below superior cervical ganglion and section of superior cardiac nerve, 3 cases.
7. Removal of the three left cervical ganglia, 11 cases.
8. Removal of the left superior and middle cervical ganglia, 12 cases.

9. Some combination of the above types, 15 cases.

10. Miscellaneous procedures on the sympathetic nerves of the neck, 35 cases.

11. Attempted section of the depressor nerve, 12 cases.

Of the 126 cases in which some one of the types of operation of the cervical sympathetic ganglia and nerves was performed complete relief of pain was reported in 50 (40 per cent), partial relief in 36 (29 per cent) and no relief in 34 (27 per cent). Results were not recorded in 6 cases. Of the 12 cases in which the cardiac depressor nerve or nerves were thought to be resected, complete relief was reported in 5 (41 per cent), partial relief in 3 (25 per cent) and no relief in 3 (25 per cent). The result was not recorded in 1 case.

Of all types, then, there was complete relief in 40.5 per cent of the cases, partial relief in 27 per cent and no relief in 26 per cent.

These results were apparently irrespective of the type of operation performed. The reason for relief is not apparent, because in no case were all of the afferent nerves resected. If we consider that the depressor nerves contain only fibers affecting the vasomotor and cardioinhibitory centers, and that the superior cervical ganglion has to do probably only with efferent fibers, it seems that all that is necessary is to break the cardiac nervous arc. Daniélopou says that similar results from section of quite different nerves proves three things: "(1) That all these nerves contain sensory cardiac fibers; (2) that cutting some of the ascending fibers, without putting them all out of action, is sufficient to benefit angina; (3) that the abolition of the ascending nerve fibers (those passing to the cervical chain), having no possible relationship with the lateral group (those passing to the dorsal ganglia), nevertheless, prevent the occurrence of the pain syndrome of angina."

Wenckebach, in 1924, was of the opinion that section of the depressor nerve would prove to be the best operation, but these statistics show that it has no advantage over the other types of operation. Moreover, the operation is more difficult and less certain. His opinion was based upon the theory of the aortic origin of angina.

During the period of observation recorded 33 patients died. Of these 8 died during the operation or within a few hours, 7 lived from two to fourteen days, 4 died in from two weeks to a month, 10 died from one month to a year and 3 lived from one to three years (time of death not reported in 1, but was apparently soon after operation). The immediate operative mortality is probably about 6.5 per cent.

With complete relief, then, in 40.5 per cent of the cases and an operative mortality in such a serious disease of only about 6.5 per cent, the operative treatment of angina would seem to be a justifiable procedure. Since 7 of the cases dying apparently as a result of operation were instances of angina due doubtless to syphilitic aortitis (out of 28 such cases in the series) it appears that that type

of angina should not be treated in this way because of the risk, even though the results in the surviving cases were comparable to those of the whole series. Eliminating the cases of angina due to syphilitic aortitis, the immediate operative mortality becomes very low, namely, 1.8 per cent, which makes the procedure appear still more justifiable.

Further examination of our series of cases, however, reveals that there are other features which detract from the efficacy of this type of therapy. Of the 129 patients who survived the operation there were 40 (31 per cent) who had disagreeable or serious postoperative complications. In other words, not only was there only partial or no relief in 53 per cent, but in 31 per cent the patients were made less comfortable. These complications were largely of the nature of pains and paresthesias of variable duration, many of which were apparently permanent, as in our case. One of the commonest types of new pain was that of pain in the side of the face, jaw or neck. Some of these had severe pain when chewing. "Brachial neuralgia" was the next most frequently observed postoperative pain. Pain in the left shoulder was present in a few cases, and in 1 case the angina switched to the right side. In no case was there pain similar to that developing in our case. Paralysis of the vocal cords occurred in 2 cases. Some of these painful complications became less intense as time went on and a few apparently disappeared, but most of them persisted. We are willing to overlook the presence of Horner's syndrome because this is always to be expected after the Jonnesco operation.

Some of the patients in this series were observed for a brief period only after operation, while others were followed for years. The longest period of observation was twelve years (case of C. H. Mayo). It is impossible, of course, to determine exactly whether the operation had any effect upon the duration of the disease, but our impression is that the course of the disease was not materially affected. We have been very lenient in arriving at the percentage of deaths due to operation. No one can say whether a number of patients who died a few days or even a few weeks after operation may not have been hurried along to the end.

We may now summarize the case for and against the operative treatment of angina pectoris: The case for this type of treatment is: (1) Complete relief of the original pain in 40.5 per cent of cases and partial relief in 27 per cent; (2) low immediate operative mortality when cases associated with syphilitic aortitis are eliminated.

The case against the operative treatment of angina pectoris is: (1) No relief or only partial relief in 53 per cent of cases; (2) post-operative appearance of annoying paresthesias, new pains or other evil complications in 31 per cent of cases; (3) effectiveness of amyl nitrite or nitroglycerin for individual attacks of pain is certainly

much more than 40.5 per cent of cases; (4) apparent absence of influence upon the course of the disease.

A few words are now appropriate concerning the treatment of cardiac pains by injection methods. Brunn and Mandl, in 1924, tried paravertebral nerve block with procain, with excellent results. Recently Swetlow began the use of alcohol in these injections. Since his pioneer work others have used this method. The results have been much more constant than with the operative treatment, and the method has more to commend it scientifically, since the visceral afferent pain fibers must eventually pass through the rami communicantes and the dorsal roots regardless of the route up to that point. White has developed the most efficient method to date. He anesthetizes the upper five thoracic nerves as a routine with an injection of 5 cc. of 1 per cent solution of procain, followed by 5 cc. of 85 per cent alcohol. Relief from pain is usually prompt and may persist for several months. There is usually some hyperesthesia for about six weeks following the injection, but this is never as severe as the pains and painful paresthesias following sympathectomy. Furthermore, there is no operative mortality. Horner's syndrome usually follows, but this is of minor importance. Transference of pain to the epigastrium, however, has been noted.

**Summary and Conclusions.** 1. The anatomy and physiology of the innervation of the heart and aorta are summarized and found to be very incompletely known.

2. The most logical theory of angina pectoris is discussed; but this, like all other theories, is merely theory.

3. A specific case of the ill-effect of cervical sympathectomy for angina pectoris is cited, in which there was severe pain in the left jaw with chewing and transference of precordial pain to the shoulders.

4. The results of the operative treatment of angina pectoris in 138 cases collected from the literature are considered.

5. Whatever stand is taken regarding the subject, it is positive that the operative treatment should not be used for angina pectoris associated with syphilitic aortitis.

6. While the immediate operative mortality is very low, there is no evidence that the course of the disease is lengthened.

7. There is only partial relief of pain or no relief at all in 53 per cent of cases. Amyl nitrite and nitroglycerin certainly give relief from individual attacks in a much larger per cent of cases than are relieved by operation.

8. Annoying paresthesias or new pains follow operation in 31 per cent of cases.

9. Alcoholic injection of the upper thoracic posterior nerve roots gives relief for substantial periods of time and is apparently free of most of the ill-effects of operation. This method of treatment deserves a fair trial.

10. The operative treatment for angina pectoris at present should be performed only in selected cases and by neurosurgeons who wish to study carefully the anatomy and physiology of the innervation of the heart and aorta and the reasons for the post-operative complications. There is considerable information which can be learned in this way which cannot possibly be obtained from dissection of the human cadaver or experiments on living animals.

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## A NEW AND SIMPLE MECHANICAL RETRACTOR FOR ABDOMINAL SURGERY.

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THE successful execution of abdominal surgical procedures depends upon (1) the skill and judgment of the surgeon, and (2) adequate exposure. Of the former consideration we shall not deal here; to the latter consideration we shall devote this paper.

To maintain exposure of the abdominal viscera, the surgeon is required either to employ hand retractors manipulated by assistants, or mechanical retractors fixed in place and allowed to remain for the duration of the operation. There is no doubt that intelligent assistance with hand retractors is very helpful during the performance of difficult surgical procedures, yet many times the physical presence and hands of the assistant hamper the surgeon and obscure his view. On the other hand, a mechanically simple and efficient instrument for abdominal retraction relieves the assistant of duties and permits him to aid the surgeon in the actual intraabdominal manipulations. He is free to hold important clamps and tissues, thus facilitating the operation.

During the past several years we have felt the need of a more efficient abdominal retractor than those which are in common use. We have employed several instruments which retract the abdominal incision from three places in a triangular manner. When this system is applied to an incision in the elastic abdominal wall it leaves a fourth side which is not restrained. The result is unbalanced forces, and it is this unbalanced system of forces which makes any three-point retraction of the abdominal wall or, for that matter any sphincter, inefficient and unsatisfactory.

We feel that an ideal instrument should retract from four dia-

metrically opposed places, and at the same time have no more than two of the retractors adjustable. These adjustable blades which, for convenience, we shall call the upper and lower angle blades, are used to retract the incision and also, by means of sterile gauze packs, to exclude viscera from the field of operation.

The conventional type of abdominal retractor has square corners which are prone to form obstruction when in use. In designing our instrument we made the side members curved (Fig. 5, 2 and 3), so that the maximum space would be inclosed within a circular

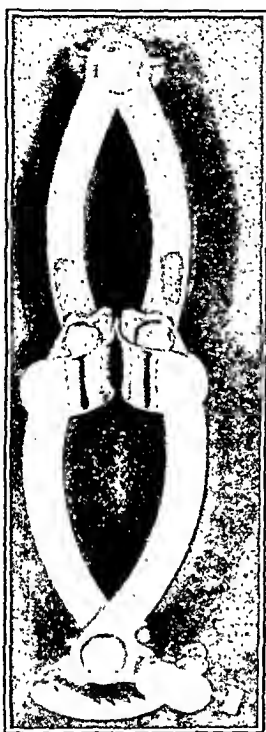


FIG. 1.—Retractor frame.  
Bottom vue closed.

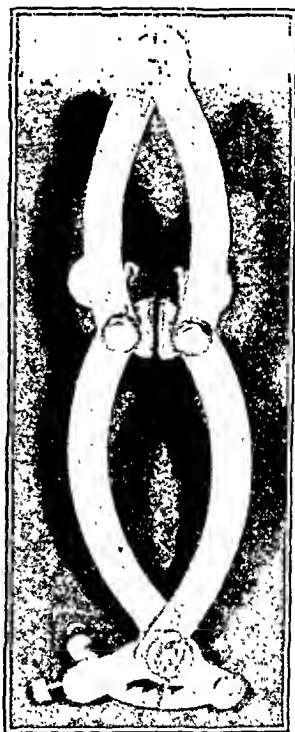


FIG. 2.—Retractor frame.  
Top vue closed.

opening, since, geometrically speaking, the circle embraces the maximum area for any given dimensions. The curved side members (Fig. 5, 2 and 3) are levers united into one unit by very strongly riveted swivelled joints. The entire frame is securely held in place so that it cannot possibly slip by means of a ratchet catch and set screw at the lower angle (Fig. 5, 5). The upper angle (Fig. 5, 1) is also secured by pressure when the upper angle retractor is fastened. The side retractors are fixed permanently to the frame. Experience has shown that too many screws and adjustable parts complicate the instrument and are a source of annoyance. The

upper and lower angle retractors (Fig. 5, 1 and 4) are detachable and slotted, and, therefore, adjustable to direct pull and a fair amount of lateral displacement. The blades are curved to restrain the incision and at the same time to hold in place deeper within the abdomen the sterile packs which restrain intruding organs which are not the subject of the particular operation.

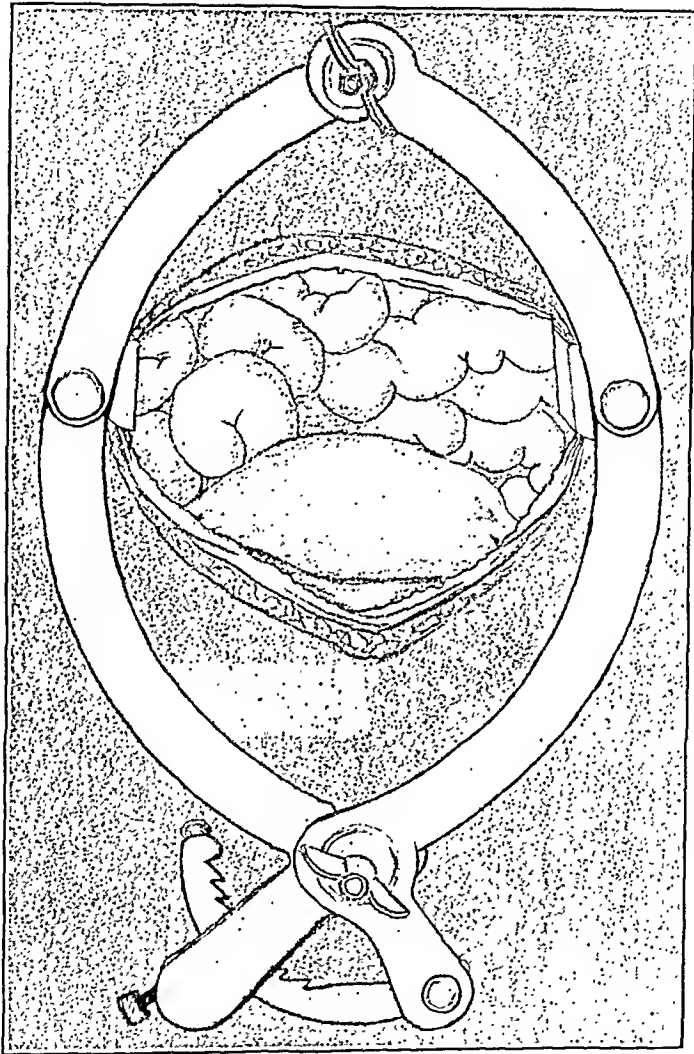


FIG. 3.—Hysterectomy. Lateral displacement of the abdominal wall by the curved side retractors the frame has been securely locked by the ratchet catch and setscrew.

So much for the technical details of this instrument. We shall now describe the modifications in abdominal technique, which Dr. O'Connor has devised for operative procedures with this instrument.

**Lower Abdominal Procedures.** *Hysterectomy, Salpingectomy.* The patient is prepared for operation in the usual routine manner.



A midline incision, about  $8\frac{1}{2}$  inches long, is made in the abdominal wall; the peritoneum is incised in the usual manner. The abdominal retractor is grasped in the right hand near the middle (Fig. 1), first one, then the other fixed side retractors are slipped into place. With both hands grasping the lower side members, the instrument is very quickly opened and then securely fastened by means of the

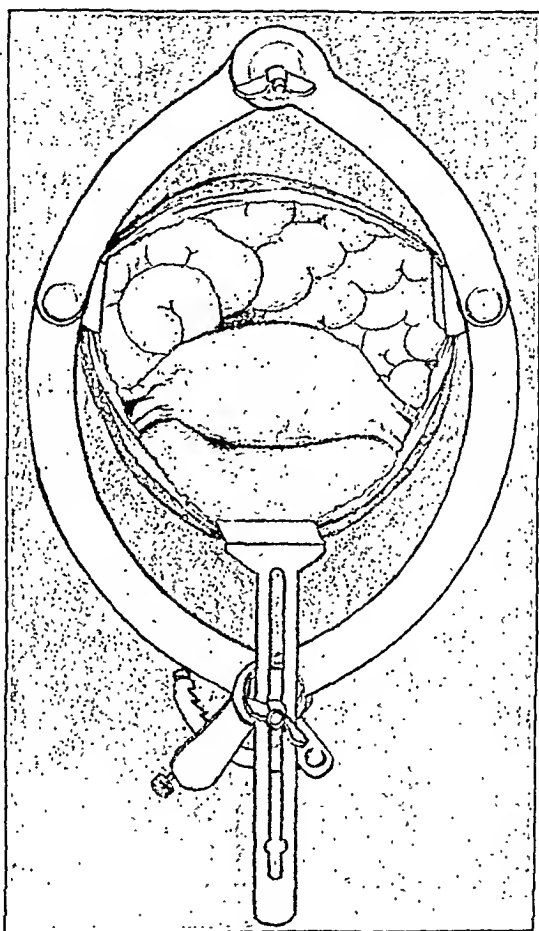


FIG. 4.—Hysterectomy. Lower angle retractor in place exposing bladder and uterus.

ratchet catch and set screw provided for that purpose (Fig. 3) at the lower angle. The patient is now placed in the Trendelenburg position, several gauze packs are slipped into the abdomen to exclude the viscera and the upper angle retractor is fastened in place with its blade restraining the packs and intestines. A thick piece of gauze, about 4 inches wide, is placed in the lower angle down to the level of the bladder and the lower angle retractor fixed in place.

With this exposure it is possible to perform quickly and with good vision the routine supravaginal hysterectomy or plastic procedures upon the tubes, ovaries or bladder.

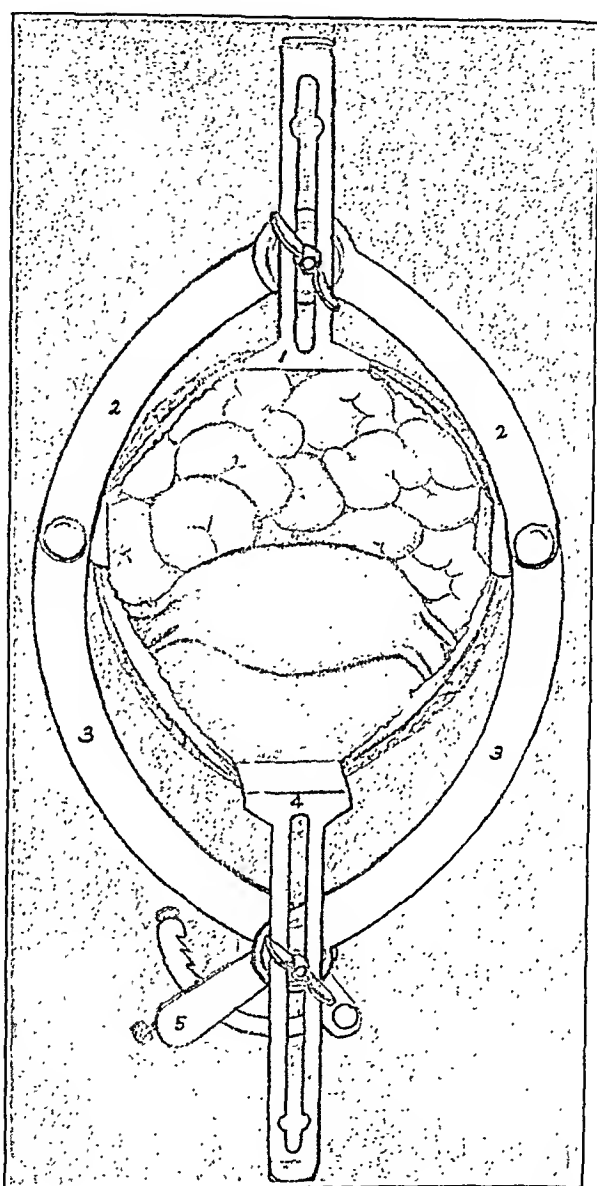


FIG. 5.—Hysterectomy. Both adjustable blades are in place showing adequate exposure obtained before the viscera are excluded by packs. No. 1. Upper angle retractor. No. 2. Upper side arms. No. 3. Lower side arms. No. 4. Lower angle retractor. No. 5. Ratchet catch and set screw.

*Rectum, Sigmoid and Colon.* The patient is placed on the table with his head slightly depressed from the horizontal and a small pillow under the sacrum. The usual median incision is made and the retractor introduced in such a manner that the long axis is

perpendicular to a line drawn through the anterior-superior spines of the ileum. Packs are then introduced to the rear of the fixed side retractor blades, then the remaining obstructing viscera are excluded by more packs and held out of the way by the adjustable retractors at the angles.

**Upper Abdominal Procedures. *Intestinal Resections.*** For an intestinal resection the same general setup is employed, with the long axis of the abdominal retractor parallel to the line connecting the superior spines of the iliac crest. The lower angle section, however (Fig. 5, 4) is on the side away from the surgeon.

***Gastroenterostomy.*** In these procedures the retractor is set with the long axis perpendicular to a line drawn across the abdomen. The end retractors and packs are not placed, however, until the surgical approach to the stomach is completed, *i. e.*, through the mesocolon and gastric omentum. Packs of gauze are then placed at the upper and lower angles and held in place by their respective retractors.

***Cholecystostomy and Cholecystectomy.*** This instrument is of greatest value in those fibrotic and densely adherent gall bladders which give the surgeon so much trouble. In these operations the side retractors are set about 2 inches below and parallel to the free border of the ribs. A pack, about 3 inches wide and some 6 inches long, is placed in the upper angle of the wound; the upper angle retractor is then placed in such a manner as to not only retract the abdominal wall but also to hold back the edge of the liver adjacent to the gall bladder. Three or four packs are now distributed in an overlapping manner to exclude the stomach duodenum and small intestine. When these steps have been accomplished and associated a very good exposure of the gall bladder and duct is obtained.

***The Retrocecal Appendix.*** To all surgeons of experience there comes from time to time the difficult retrocecal appendix. In an obese individual the appendix which is deeply retrocecal and bound down with fibrous adhesions and gangrene presents a very difficult procedure to remove without breaking the appendix and liberating its dangerous contents into the peritoneal cavity. When this retractor is fixed in place it gives good exposure which greatly facilitates the operation.

**Conclusions.** With this instrument, it is possible to see the field of operation more clearly in abdominal operations. It secures the abdominal wall so that the surgeon may use his assistant during the more difficult phases of the intraabdominal manipulations. The design of this instrument is simple. It is easily applied and gives positive exposure without slipping.

## THE SPECIFIC DYNAMIC ACTION OF FOOD IN ABNORMAL STATES OF NUTRITION.

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IN investigations of the metabolic properties of abnormal nutritional states much attention has been given to the possibilities of variations in the specific dynamic action of foods which might characteristically be associated with such states. The reports of many observers<sup>5,25,27,36</sup> suggest that a definite relationship exists between obesity and an abnormality in the specific dynamic action of food. Mason<sup>24</sup> reported that thin states are also associated with an abnormal action. Although Aub and DuBois<sup>3</sup> showed many years ago that the specific dynamic action in persons of unusual shape was normal, Gibbons<sup>16</sup> found a difference between 2 dogs of the same weight but of different shapes. Some investigators<sup>1,15,27</sup> appear to find large variations in specific dynamic action in pathologic conditions which are frequently associated with abnormal nutritional states, whereas essentially normal results have been found by other authors<sup>4,13,26</sup> in *analogous nutritional disturbances*.

Many of the phenomena associated with the heat effects of foods have been studied in detail. The present knowledge relative to the extra heat production by the various food types is reviewed by Lusk,<sup>23</sup> who draws particular attention to the constancy of this action. With regard to protein, by far the most important food substance in this respect, Rapport and Beard<sup>29</sup> conclude: "That the specific dynamic action of protein is fully accounted for by the summated specific dynamic actions of their constituent amino acids." Rapport<sup>28</sup> has also demonstrated a constant increase of heat production following the ingestion of equal quantities of glycine by different dogs. If these observations be true the development of different heat quantities from the same food by persons who differ only in their food reserves represents an anomalous situation. It seems, therefore, desirable to reëxamine the problem of the abnormalities of specific dynamic action which may be encountered in thin and obese states.

**Methods.** Three groups of subjects were investigated with reference to the heat effect produced by a fixed meal. Eighteen persons were classified into 5 normal, 5 thin, 8 obese. After variable periods of training in taking basal metabolic determinations the subjects were given a test meal which was eaten in 20 minutes or less. The meal consisted of: Boiled egg, 50 gm.; egg white, 50 gm.; cream, 25 gm.; milk, 200 gm.; sugar, 5 gm.; orange, 70 gm.; bread, 30 gm.; oatmeal, 20 gm.; water, 100 gm.; chicken, 54 gm.; butter, 6 gm.

The total values for this food, as calculated from the tables of Atwater and Bryant<sup>2</sup> are: Protein, 40 gm.; carbohydrate, 52 gm.; fat, 26 gm. The total calories are estimated as 610, with 160 (26 per cent) from protein. The entire meal was eaten by each subject. Metabolism determinations were made before the meal and 1, 2, 3, 4, 6 and 8 hours after the conclusion of the meal. Throughout the test the activities of the patients were restricted. Between tests, for the most part, they sat reading in bed or in a chair. A limited amount of walking around the room was permitted in the interests of comfort. However, before each determination, the customary 20-minute period of relaxation in bed was observed. The heat of metabolism was determined indirectly by the Tissot apparatus. The simultaneous nitrogen output in the urine was not determined and the caloric values were calculated from the uncorrected respiratory quotients.

**Observations.** Twenty-five determinations were made upon 18 subjects. The essential descriptive data of each subject are summarized in Table 1.

Of the 25 determinations 15 have been considered as having sufficient technical accuracy to warrant analysis. The standards of admissibility which are admittedly rather exacting are: (1) The caloric value for the basal state on the test day must vary by less than 2 calories from the average basal calories of the several determinations performed within 14 days before or after the test; (2) the total heat effect of the meal, as determined from the graphs, must differ from the average value for the particular group by less than four times the average deviation of the mean of the group.<sup>17</sup> Six tests were made upon 5 normal persons. Five of these were satisfactory. Fourteen tests were made upon 8 obese persons and 7 tests on 5 persons were satisfactory. Most of these patients were undergoing reduction of weight according to the dietary principles which have been described elsewhere.<sup>33</sup> Three satisfactory tests were made on 3 of the 5 underweight patients. A summary of the successful and of the unsuccessful determinations appears in Table 2.

The observations of the total calories per hour which were obtained in each group are summarized in Table 3. For the sake of completeness the data on the 10 determinations which were excluded from the averages are given at the bottom of the table.

TABLE 1.—ESSENTIAL DESCRIPTIVE DATA OF SUBJECTS BY GROUPS.

Test.	Date.	Sex.	Age.	Height, inches.	Weight, pounds.	Ideal weight, pounds.	Excess weight, per cent.	Surface, sq. m.	Ideal surface, sq. m.	Excess surface, per cent.
<i>Normal.</i>										
2 . .	Dec. 14, 1928	F	23	64 $\frac{1}{2}$	135 $\frac{1}{2}$	130	4	1.67	1.64	2
17 . .	May 24, 1929	F	23	64 $\frac{1}{2}$	134	130	3	1.65	1.64	1
4 . .	Feb. 1, 1929	M	34	69 $\frac{1}{2}$	150 $\frac{1}{2}$	160	- 6	1.83	1.89	- 4
20 . .	April 18, 1930	F	21	60 $\frac{1}{2}$	111 $\frac{1}{2}$	116	- 4	1.47	1.48	- 1
21 . .	April 19, 1930	F	21	65 $\frac{1}{2}$	137	129	6	1.68	1.65	2
<i>Obese.</i>										
1 . .	Dec. 6, 1928	F	30	60 $\frac{1}{2}$	145	122	18	1.63	1.52	7
7 . .	Mar. 15, 1929	F	39	62 $\frac{1}{2}$	344 $\frac{3}{4}$	133	159	2.42	1.62	49
24 . .	Aug. 22, 1930	F	40	62 $\frac{1}{2}$	215 $\frac{1}{2}$	133	62	1.99	1.62	23
6* . .	Feb. 24, 1929	M	37	66 $\frac{3}{4}$	146 $\frac{3}{4}$					
12** .	April 12, 1929	F	39	63 $\frac{1}{2}$	230	136	69	2.06	1.65	25
14 . .	April 26, 1929	F	39	63 $\frac{1}{2}$	222	136	63	2.04	1.65	23
25 . .	Sept. 17, 1930	F	25	67 $\frac{1}{2}$	201 $\frac{3}{4}$	142	42	2.03	1.76	15
<i>Thin.</i>										
9 . .	April 5, 1929	F	25	67	117	139	-16	1.61	1.73	- 7
11 . .	April 12, 1929	M	24	70 $\frac{1}{2}$	127 $\frac{1}{2}$	158	-20	1.73	1.90	- 9
23 . .	June 6, 1930	F	21	65	109 $\frac{1}{2}$	129	-15	1.54	1.64	- 6
<i>Unacceptable.</i>										
5 . .	Feb. 8, 1929	F	39	62 $\frac{1}{2}$	376 $\frac{1}{2}$	133	183	2.52	1.62	55
8 . .	Mar. 29, 1929	F	45	64 $\frac{1}{2}$	239	143	67	2.12	1.71	24
22 . .	April 30, 1930	F	21	63	102	123	-21	1.45	1.57	- 8
15 . .	May 17, 1929	F	39	62 $\frac{1}{2}$	305 $\frac{1}{2}$	133	130	2.30	1.62	42
10 . .	April 5, 1929	F	52	65 $\frac{1}{2}$	211	148	43	2.03	1.75	16
3 . .	Jan. 20, 1929	F	20	63 $\frac{3}{4}$	143	128	12	1.71	1.63	5
13 . .	April 26, 1929	F	39	62 $\frac{1}{2}$	325	133	144	2.37	1.62	46
16 . .	May 17, 1929	F	39	63 $\frac{1}{2}$	213	136	57	2.00	1.65	21
18 . .	June 14, 1929	F	31	56	195 $\frac{3}{4}$	113	73	1.76	1.39	27
19 . .	Feb. 7, 1930	M	28	66 $\frac{1}{2}$	109 $\frac{1}{2}$	145	-25	1.56	1.80	-13

\* Amputation.

\*\* Acromegaly.

TABLE 2.—SUMMARY OF ACCEPTABLE AND UNACCEPTABLE TESTS.

Group.	Acceptable tests.	Unacceptable tests.					
		Base line.			Total calories.		
		Too high.	Too low.	Total.	Too high.	Too low.	Total.
Normal . . . . .	5	...	...	...	...	1	1
Obese . . . . .	7	2	1	3	2		4
Thin . . . . .	3	2	...	2			
Total . . . . .	15			5			5

TABLE 3.—TOTAL CALORIES PER HOUR—BASAL AND AFTER TEST MEAL.

Tcst.	Basal cal.	First hour.		Second hour.		Third hour.		Fourth hour.		Sixth hour.		Eighth hour.	
		Cal.	Inc.	Cal.	Inc.	Cal.	Inc.	Cal.	Inc.	Cal.	Inc.	Cal.	Inc.
Normal.													
2 . . .	57.0	71.9	14.9	68.9	11.9	67.5	10.5	65.1	8.1				
17 . . .	54.1	66.0	11.9	65.2	11.1	63.0	8.9	59.7	5.6	56.6	2.5	52.6	-1.5
4 . . .	70.4	84.9	14.5	77.8	7.4	73.9	8.5	77.3	6.9	69.0	-1.4	69.2	-1.2
20 . . .	51.1	60.2	9.1	59.1	8.0	60.9	9.8	60.3	9.2	57.4	6.3	55.8	4.7
21 . . .	58.6	66.5	7.9	65.3	6.7	66.0	7.4	62.9	4.3	62.0	3.4	63.4	4.8
Ave. . .	58.2	...	11.7	...	9.0	...	9.0	...	6.8	...	2.1	...	1.3
Obese.													
1 . . .	59.9	66.6	6.7	72.1	12.2	69.0	9.1	67.8	7.9				
7 . . .	91.2	97.0	5.8	96.0	4.8	95.5	4.3	102.0	10.8	97.5	6.3	87.0	-4.2
24 . . .	67.6	77.0	9.4	82.3	14.7	77.8	10.2	73.3	5.7	72.0	4.4	69.0	1.4
6 . . .	64.8	77.5	12.7	73.5	8.7	75.0	10.2	71.5	6.7	62.2	-2.6	59.8	-5.0
12 . . .	82.5	97.0	14.5	97.2	14.7	95.5	13.0	94.6	12.1	84.6	2.1	85.1	2.6
14 . . .	77.7	89.3	11.6	95.9	18.2	91.6	13.9	88.0	10.3	82.1	4.4	94.8*	16.1*
25 . . .	56.1	70.0	13.9	68.0	11.9	66.5	10.4	66.5	10.4	62.0	5.9	56.0	-0.1
Ave. . .	71.4	...	10.7	...	12.2	...	10.2	...	9.1	...	3.4	...	-0.8
Thin.													
9 . . .	60.2	70.8	10.6	76.5	16.3	68.4	8.2	67.9	7.7	67.0	6.8	61.9	1.7
11 . . .	60.6	73.9	13.3	68.7	8.1	65.0	4.4	72.9	12.3	64.0	3.4	63.6	3.0
23 . . .	47.4	63.8	16.4	61.0	13.6	56.9	9.5	58.5	11.1	54.1	6.7	54.8	7.4
Ave. . .	56.1	...	13.4	...	12.6	...	7.4	...	10.4	...	5.6	...	4.0
Unacceptable.													
5 . . .	100.0	106.0	6.0	103.5	3.5	107.7	7.7	102.0	2.0	94.0	-6.0	92.1	-7.9
8 . . .	70.7	77.9	7.2	81.0	10.3	78.7	8.1	77.1	6.4	75.4	4.7	66.5	-4.2
22 . . .	47.2	58.4	11.2	58.3	11.1	55.0	7.8	56.8	9.6	56.5	9.3	54.0	6.8
15 . . .	82.2	83.2	1.0	87.0	4.8	80.4	-1.8	83.8	1.6	84.0	1.8	76.0	-6.2
10 . . .	67.3	69.3	2.0	69.2	1.9	70.0	2.7	67.6	0.3	68.0	0.7	58.2	-9.1
3 . . .	66.5	80.5	14.0	74.6	8.1	68.8	2.3	66.8	0.3	65.0	-1.5	62.0	-4.5
13 . . .	76.9	91.0	14.1	91.5	14.6	100.0	23.1	102.0	25.3	90.6	13.7	89.6	12.7
16 . . .	66.8	87.0	20.2	81.1	14.3	81.9	15.1	83.4	16.6	77.2	10.4	72.6	5.8
18 . . .	48.8	61.2	12.4	61.5	12.7	63.2	14.4	63.9	15.1	58.5	9.7	55.6	6.8
19 . . .	51.1	66.3	15.2	68.8	17.7	69.8	18.7	68.1	17.0	56.5	5.4	55.4	4.3

\* Omitted.

It may be noted that the average of the basal calories for the normal group, 58.2, is well within the usual range. The obese group has a slightly higher figure, 71.4, as is to be expected.<sup>32</sup> The average for the thin group is 56.1 calories, which is slightly lower than the normal group but not unusual for such patients. The influence of the test meal upon the total calories per hour is summarized in Columns 2 to 13 above. The figures for each hour in each group are averaged separately for purposes of comparison. It may be noted that the maximum caloric increment in the normal group is 11.7 calories above a base line of 58.2 calories per hour. In the obese group the maximum level is 12.2 calories above a base line of 71.4 calories per hour. The thin group has a maximum of 13.4 calories over the base line of 56.1 calories per hour.

It is customary in metabolic work to express observations in terms of "basal metabolic rate." The attention is thereby focussed not

upon the actual heat production, which is truly a rate, but upon the ratio of the observed rate to the rate of an average individual of the same sex, age and surface. This ratio popularly designated "basal metabolic rate" is generally of great practical value. The effect of food ingestion upon this ratio has been calculated and the results are summarized in Table 4. The usual terminology is employed.

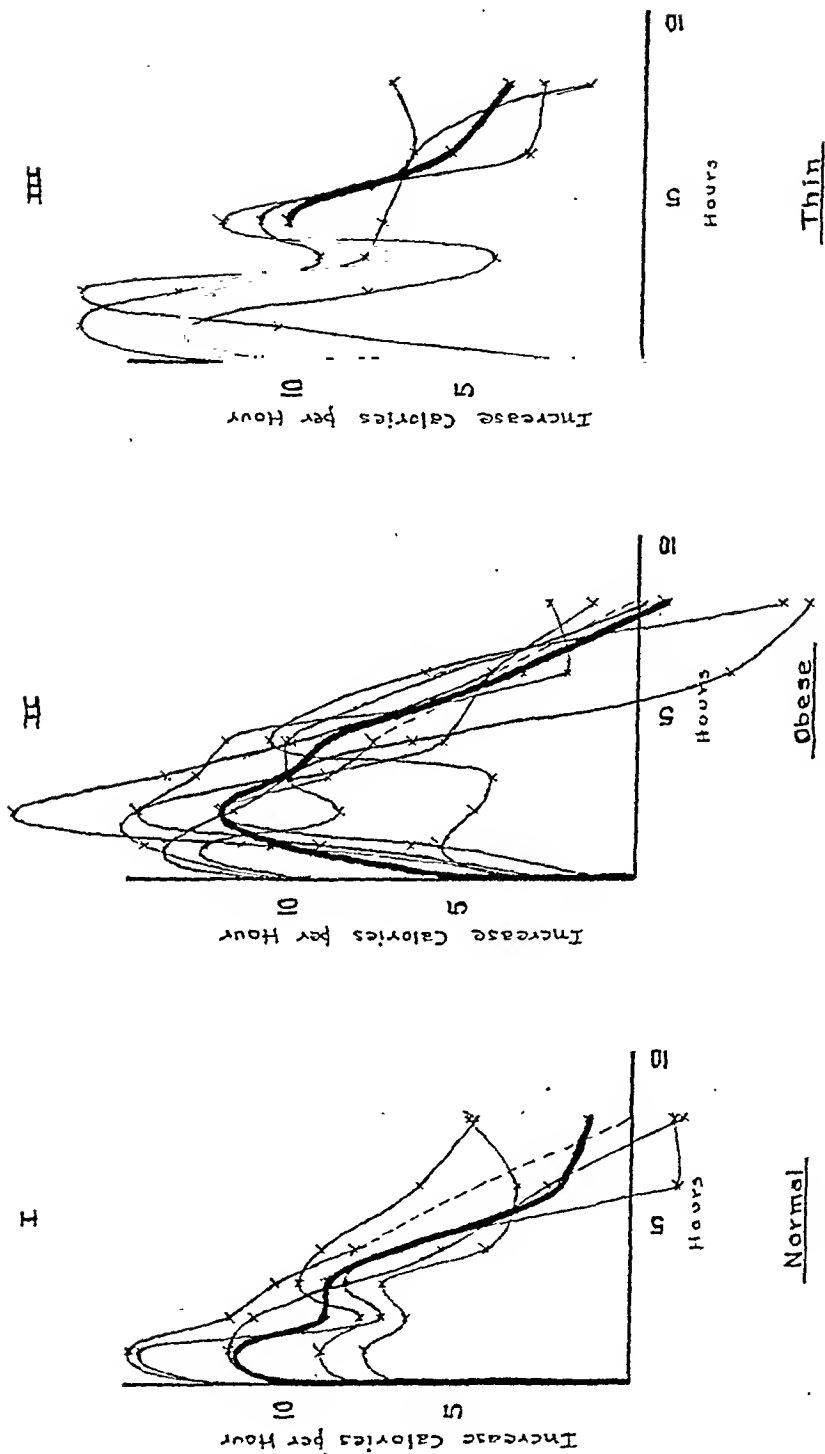
TABLE 4.—CHANGES IN BASAL METABOLIC RATE BASED UPON ACTUAL SURFACE.

Test.	Basal metabolic rate, per cent.	Increase over basal metabolic rate.					
		First hour, per cent.	Second hour, per cent.	Third hour, per cent.	Fourth hour, per cent.	Sixth hour, per cent.	Eighth hour, per cent.
<i>Normal.</i>							
2 . . . . .	- 7.9	24.4	19.4	17.1	13.3		
17 . . . . .	-11.4	19.5	18.2	14.6	9.2	4.1	-2.4
4 . . . . .	- 2.5	18.4	10.0	11.4	9.3	-2.0	-1.8
20 . . . . .	- 6.0	16.7	14.7	18.0	16.9	11.5	8.6
21 . . . . .	- 6.3	12.7	10.7	11.8	6.9	5.6	7.7
Ave. . . . .	- 6.8	18.3	14.6	14.6	11.1	4.8	3.0
<i>Obese.</i>							
1 . . . . .	0.5	11.5	20.9	15.4	13.2		
7 . . . . .	3.0	6.9	5.8	5.2	12.9	7.4	-4.4
24 . . . . .	- 5.7	13.2	20.6	14.3	8.0	6.2	2.0
6*							
12 . . . . .	9.7	19.3	19.6	17.3	16.1	3.1	3.5
14 . . . . .	4.4	15.6	24.4	18.6	13.8	5.9	24.9*
25 . . . . .	-25.2	18.4	15.7	13.7	13.7	8.2	-0.2
Ave. . . . .	- 2.2	14.1	17.8	14.1	12.9	6.2	0.2
<i>Thin.</i>							
9 . . . . .	1.1	14.9	27.3	13.5	13.0	11.3	2.9
11 . . . . .	-11.4	19.6	11.9	6.5	18.1	5.1	4.5
23 . . . . .	-16.8	28.8	23.9	16.7	19.5	11.8	13.0
Ave. . . . .	- 9.0	21.1	21.0	12.2	16.9	9.4	6.8

\* Omitted.

The average figure for the basal rate for the normal group is -6.8 per cent, with relatively slight individual deviation from the average. The obese group when calculated in the conventional manner averages -2.2 per cent. The sole marked variant being Patient 25. It should be noted that this woman was healthy, young, obese, but in no sense pathologic. The thin group showed an average basal metabolic rate slightly lower than the other two groups, -9 per cent. The influence of the test meal upon the basal metabolic rate and when calculated in the same manner is shown in Columns 3 to 8 of Table 4. The normal group shows an average rise in the first hour of 18 per cent, with a range from 12 to 24 per cent. In the





CHARTS I to III.—Heat effect of test meal.

second and third hours the effect is somewhat lessened with the more rapid drop starting at the fourth hour. At the end of 8 hours the average value was still 3 per cent above the initial level. The figures for the obese group show a somewhat less rapid rise, with a maximum in the second hour and a complete return to normal in 8 hours. In this series, although individual patients (1 and 7) showed relatively less change in the first hour or two, the average peak value, 18 per cent, is as great as that observed in the normal group, although somewhat delayed. The extreme variants in the second hour are 24 and 6 per cent. The thin patients show a percentage rise which is slightly higher than the normals—maximum, 21 per cent. There is a rapid drop at the third hour, with a secondary rise and a failure to return to the base line at the eighth hour by 7 per cent. The individual observations in the first hour vary from 12 to 29 per cent.

Of greater significance than these comparisons of total calories per hour and of metabolic rates, are those of the total heat effects which are made possible by a consideration of the originally noted differences in total calories per hour. The simplest method is to plot the observations of times and caloric increments as ordinates and abscissæ respectively. A smooth curve drawn through these points approximates most reasonably the probable changes in rate of heat production. Consequently, the area beneath the curve represents the total heat production in the observed time interval. The data from Table 3 have been plotted in the following charts, the heavy line in each case representing the composite curve for the group.

The heat production as derived from the areas beneath these curves is summarized in Table 5:

The total heat production for the normal group averages 51 calories in 8 hours. The obese group produced 58 calories in 8 hours and the thin group 67 calories. If only the first four hours are considered the three groups show an even closer agreement, or 37, 42 and 43 calories respectively. The average of all 15 determinations is 57 calories in 8 hours, or 41 calories in 4 hours.

From these data it is possible to calculate the actual percentage increase in heat production, *i. e.*, the number of extra calories produced in 8 hours divided by the number of basal calories for 8 hours, assuming a constant base line. This form of calculation gives an average increase of 11, 10 and 15 per cent in the normal, obese and thin groups respectively. (Column 12, Table 5.)

**Discussion.** *Types of Subjects.* The patients were classified according to their variations from their probable ideal weights. A variation of less than 15 per cent from the ideal weight was considered within normal limits. Obesity was defined as weight more than 15 per cent in excess of normal. The observed weights ranged from 18 to 160 per cent above the ideal weights. Certain authors<sup>22, 27</sup>

regard the obese state as divisible into groups on the basis of secondary characteristics which are alleged to indicate the etiology of the condition in the given case. Exogenous and hypopituitary types are commonly mentioned. Plaut<sup>27</sup> concludes that, in addition to their less tangible definitive properties, these types may be separated upon the basis of differences in the specific dynamic action to food. Although we are unable to differentiate the several types of the obese state, our group of obese patients showed a

TABLE 5.—EXTRA CALORIES PRODUCED BY TEST MEAL—INTERPOLATED FROM GRAPH.

Test.	Calories produced.						Total calories.	First four hours.	Second four hours.	Basal calories for eight hours.	Increase in basal calories, per cent.
	First hour.	Second hour.	Third hour.	Fourth hour.	Sixth hour.	Eighth hour.					
							<i>Normal.</i>				
2 . . .	11	14	11	9	11*	3*	59	45	14	456	13
17 . . .	10	12	10	7	8	2	49	39	10	433	11
4 . . .	13	11	8	8	5	0	44	40	5	563	8
20 . . .	8	9	9	10	16	11	61	36	27	409	15
21 . . .	7	7	7	6	8	8	43	27	16	469	9
Ave. . .	10	11	9	8	8	5	51	37	14	466	11
							<i>Obese.</i>				
1 . . .	3	11	11	9	11*	4*	48	34	15	479	10
7 . . .	5	6	5	8	18	4	45	24	22	730	6
24 . . .	6	13	13	8	10	6	55	40	16	541	10
6 . . .	12	10	10	9	4	0	44	41	4	518	8
12 . . .	14	15	14	13	14	4	74	56	18	660	11
14 . . .	6	17	17	12	14	4*	69	52	18	622	11
25 . . .	13	13	11	10	17	6	69	47	23	449	15
Ave. . .	8	12	12	10	13	4	58	42	17	571	10
							<i>Thin.</i>				
9 . . .	6	15	12	8	14	9	63	41	23	482	13
11 . . .	12	11	6	8	16	6	59	37	22	485	12
23 . . .	16	15	11	10	18	7*	78	52	25	379	20
Ave. . .	11	14	10	9	16	7	67	43	23	449	15

\* From corrected curve.

greatly varied and representative list of secondary characteristics. Both sexes were represented. Young and old individuals were present. A perfect example of the so-called "hypopituitary" type was included as well as a fully developed case of acromegaly who was likewise obese. One subject lacked a leg as a result of an old mid-thigh amputation. Our observations show that, regardless of their varying characteristics, obese persons react in the same manner to a test meal. This opinion is in accord with that of Lanter,<sup>21</sup> who failed to differentiate "exogenous," "hypopituitary" and

"hypothyroid" types on the basis of specific dynamic action to food. The finding of the usual specific dynamic action in a aeromegalie is especially noteworthy. The findings of Aub and DuBois<sup>3</sup> of normal metabolic reactions in individuals having artificially diminished surfaces are also supported.

The thin patients were by definition more than 15 per cent below their normal weight, ranging in this series from 15 to 20 per cent. Mason<sup>24</sup> found a definitely increased percentage reaction in thin subjects, and believed this factor to be of importance in the etiology of the condition. Our observations fail to determine a significant deviation from the normal food reaction. Of considerable interest is the fact that Patient 11, who was 24 years of age, had an advanced chronic nephritis. He gave a perfectly normal heat reaction, thereby suggesting that the anomaly of protein metabolism, which is characteristic of nephritis, is not manifest at these earliest stages in protein utilization.

*Test Meals.* The test meals which have been used by previous workers have been extremely varied. As a rule, since the effect of protein alone was under consideration, high-protein meals consisting of 150 to 200 gm. of lean beef alone, or accompanied by bread, have been used. Some of the earlier investigations have used 400 to 600 gm. of lean beef, and in view of the fact that the object of most of these studies was the determination of the maximum effect producible upon the metabolic rate, such meals were eminently satisfactory. A summary of a few of the test meals which have been used appears in Table 6:

TABLE 6.—TEST MEALS AND DURATION OF TESTS.

Author.	Reference No.	Duration, hours.	Test meal.
Appel and Farr . . . . .	1	2	200 gm. meat, 1 slice bread and butter.
Aub and DuBois . . . . .	3	4 to 7	660 gm. scraped beef, small amount of potatoes, kaffee hag.
Aub and Means . . . . .	4	5	350 to 500 gm. beef cooked with butter, tomato, water.
Benedict and Carpenter . . . . .	7	3 to 7	200 gm. meat (150 to 360).
DuBois . . . . .	13	...	10 gm. nitrogen as egg albumen, casein or meat.
Gibbons . . . . .	16	6	200 gm. meat.
Lauter . . . . .	21	6½ to 8½	200 gm. beef, 50 gm. bread.
Liebschutz-Plaut, Schadow . . . . .	22	1	200 gm. meat, 200 gm. bread, 100 gm. fat.
Mason . . . . .	24	4	200 gm. beef.
Mason . . . . .	25	4	150 to 200 gm. beef.
Means . . . . .	26	3	150 to 200 gm. beef.
Plaut . . . . .	27	3	200 gm. meat, 50 gm. fat, 200 gm. bread, ½ liter coffee, occasionally milk and egg white.
Wang, Strouse, Saunders . . . . .	36	8	32 to 78 gm. protein as scraped beef, 1 to 2 glasses milk, 2 slices bread, 1 piece butter.

In addition to the great variety of meals employed which prohibits the comparison of their heat effects, many authors record considerable variation in the amount ingested by different subjects in the same series. Wang, Strouse and Saunders,<sup>36</sup> for example, record variations of protein intake between 32 and 66 gm. More important, however, is the fact that average protein ingestion in their obese series was one-third less and in the thin group one-fourth less than in the normal series. Such variations introduce into the analysis the problem of the additive nature of successive increases in protein intake. Benedict and Carpenter,<sup>7</sup> DuBois<sup>12</sup> and Lusk<sup>23</sup> discuss the experiments of Gigon and others in this connection. Kraus and Rettig<sup>20</sup> question if the specific dynamic action of foods is always strictly additive. As the solution of this problem may still be considered as unsettled, it seems highly desirable to require the ingestion of identical test meals by all subjects.

However, the determination of the total heat effect of a meal presupposes the complete digestion and absorption of the meal in the period of observation. Hawk and his coworkers<sup>18</sup> have shown that the normal period of complete emptying of the stomach for 100 gm. of beef averages 3 hours, with a variation from  $2\frac{1}{2}$  hours in the fast types to  $3\frac{1}{2}$  hours in the slow. It seems reasonable to suppose, therefore, that many of the test meals which have been used were not completely out of the stomach in the 2- to 4-hour periods of observation. Kraus and Rettig<sup>20</sup> have critically discussed this point, and in their series were able to demonstrate by Roentgen ray examination the complete emptying of the stomach in  $4\frac{1}{2}$  hours, using, however, only about 30 gm. of protein. Another factor of importance seems to be the appetizing quality of the meal. Although Hawk<sup>19</sup> has shown that once food is ingested successfully it is probably entirely digested, the importance of the psychic control of digestion, especially with reference to the secretion of proteolytic digestive juices is well established. Such psychic factors might appreciably influence the prompt handling of meals designedly high in protein. Our meal was, therefore, intended to supply the desired protein in an appetizing form and minimize the emotional stress with its own independent heat effect consequent to the forced ingestion of apparently large quantities of unfamiliar foods. At the same time it was important that these foods should leave the stomach promptly, particularly in view of our inability to control complete emptying by Roentgen ray observation. The employment of a mixed meal seemed a requisite for the inclusion of these factors. It may be stated that the components of the meals were weighed on a balance to the nearest 0.1 gm. and that each patient ate the entire quantity in less than 20 minutes. Under these conditions it seems probable that the factors responsible for the extra heat production<sup>23,29</sup> were quantitatively reproduced in each patient.

*Base Line.* The most vital observation for a successful test is the base line of the curves. This fact becomes obvious when it is recalled that all other determinations are referred to this base. In spite of the obvious importance of the base-line determination few of the recent workers have attempted to insure representative basal caloric values. Some papers mention a single trial basal on the preceding day. Other articles imply no preliminary training. Many of the unusual values which have been reported might perhaps be explained on this basis. Benedict and Carpenter<sup>7</sup> devote many pages to the exhaustive discussion of this point. Attention is called to the normal daily variations in the basal calories. They point out the irrationality of the interpolation of a base line from one day to the next, and after a discussion of the proper basal value to use decide<sup>8</sup> “. . . that the determination of basal values immediately prior to the ingestion of food is the most logical and satisfactory method for studying the small changes in metabolism frequently noted after the ingestion of food.” We have adopted this point of view.

Standard metabolic practice requires that a basal determination be performed at least 8 hours after the last meal. High-protein meals require a longer interval before the postabsorptive state is reached. Our series of patients received their basal test 14 to 16 hours after their last meal. In view of the Roentgen ray studies of Kraus and Rettig<sup>20</sup> and of our own heat studies, this period practically insures a true postabsorptive state even for patients who are kept on a “maintenance protein diet” for reduction purposes.

In our experience an adequate training of the patient is essential to securing a correct basal determination on a given test day. Failure in our earliest tests to fully appreciate the importance of this factor is an important cause for their inclusion in our group of unsatisfactory tests. Only one of the three tests made after only one or two preliminary basal determinations was satisfactory. The recent practice has been to perform a series of basal determinations at intervals of 1 to 7 days until the results were approximately uniform. In several of the most recent tests two basal determinations were performed on the subject on the morning of the test in addition to the prolonged training period. The second determination was employed in the calculations, the first being included in the practice period. Again, after the completion of the test one or more basal determinations were made at intervals to check the base line. Many patients who were trained specifically for this purpose of this test had five to seven preliminary tests. The majority were subjects under other investigations and received weekly basals for many weeks.

The first criterion for inclusion of a test in the acceptable group, as described above, permits a variation of the test day basal by 2 calories from the average. Since all of the obese and 1 of the

thin patients were undergoing weight alterations by dietary procedures, with the inseparable alterations in basal metabolic level,<sup>32</sup> the average value used for comparison includes only the determinations made within 14 days before or after the test day. The value of the training period is shown in Table 7, which records the deviation of the basal calories from the average of the recent determinations.

TABLE 7.—DEVIATION OF BASE LINE FROM THE AVERAGE OF TRIAL DETERMINATIONS.

Test.	Number of determinations.	Average calories per hour.	Difference from test day.
<i>Normal.</i>			
2 . . . . .	3	57.4	0.4
17 . . . . .	1	54.1	0.0
4 . . . . .			
20 . . . . .	4	51.4	0.4
21 . . . . .	5	57.1	0.4
<i>Obese.</i>			
1 . . . . .	4	59.5	0.4
7 . . . . .	4	90.4	0.8
24 . . . . .	4	66.4	1.2
6 . . . . .	3	63.1	1.7
12 . . . . .	5	82.1	0.4
14 . . . . .	6	78.1	0.4
25 . . . . .	4	55.6	0.5
<i>Thin.</i>			
9 . . . . .	3	60.9	0.7
11 . . . . .	5	59.9	0.7
23 . . . . .	4	47.1	0.3
<i>Unacceptable.</i>			
5 . . . . .	3	97.9	2.1
8 . . . . .	4	67.4	3.3
16 . . . . .	3	69.2	2.4
19 . . . . .	6	53.2	2.1
22 . . . . .	4	44.9	2.3
3 . . . . .	2	66.0	0.5
10 . . . . .	2	67.6	0.3
13 . . . . .	3	78.4	1.5
15 . . . . .	4	80.8	1.4
18 . . . . .	4	49.7	1.1

It will be seen from these data that the average deviation of the fifteen acceptable tests is 0.6 calorie and that only two values are greater than 1 calorie. An agreement of this order invites confidence in the reliability of the all-important basal determination and its dependent data.

The depression of the basal level of heat production after a meal has been noted by Lauter<sup>21</sup> and Bernhardt.<sup>11</sup> Benedict and Carpenter<sup>7</sup> state that they have never encountered this phenomenon. Bernhardt discussed this "negative phase" after food, but more especially after work, at considerable length. He emphasized that the negative phase after food was found only in subjects having high basal levels. Two of our normal and 3 of the obese patients

showed this depression. In 1 normal No. 17 and 1 obese No. 25 subject the curve passed below the base line after  $7\frac{1}{2}$  hours and the net caloric effect was less than 1 calorie in 8 hours. The curve of the second normal No. 4 cut the base line at 6 hours and flattened out, giving a possible heat effect of 2.5 calories. The curve of No. 6 crossed the base line at  $5\frac{1}{2}$  hours and apparently showed a negative heat effect of 8 calories, while No. 7 crossed at  $7\frac{1}{2}$  hours with a heat effect of 1 calorie. The 3 patients on whom base-line data are complete No. 6, 7, 25 all showed an elevation of the base line on the day of the test above the average base line. In fact, No. 6, who had the only significant depression, deviated from the average base line by 1.7 calories. It is likewise worthy of note that the total calories under the three significantly depressed curves fall among the lower values of their respective groups.

Of the ten unacceptable curves 5 curves pass below the base line. Of these five curves a demonstrable abnormally high base line was directly responsible for the discarding of two (obese) in spite of the fact that the total heat effect in each case was within acceptable limits. Two other curves, one normal and one obese, which were discarded because the total heat effect was grossly too low, were performed on untrained patients. The fifth curve of this group, which was the fourth specific dynamic action test of a series of five on the same patient (see below), showed two negative phases, at the third hour and again at the seventh hour respectively. Here again a correction of the base line practically nullifies the negative phases. In general, therefore, it may be stated that ten of our twenty-five curves showed some degree of negative phase. Only five were found on technically acceptable determinations. In only two of these was the negative phase greater than 1 calorie, both being associated with high base lines. Only one curve acceptable or unacceptable showed a negative phase when the base line was below the average basal calories, and this was a grossly abnormal curve performed on an untrained subject. Therefore, in accord with Benedict and Carpenter we are unable to demonstrate that the "negative phase" exists as a real phenomenon except insofar as it measures the abnormal elevation of the base line.

*The Percentage of Specific Dynamic Action.* Throughout medical literature the heat influence of food is expressed in terms of percentage. An attempt to compare the results of different observers shows at once that the meaning to be attached to this percentage factor varies considerably. Certain authors fail to clearly define the ratios employed. Other authors refer to the algebraic difference in percentage of the metabolic rate after food, as compared with the percentage of basal metabolic rate. Mason<sup>25</sup> and Wang, Strouse and Saunders<sup>36</sup> reduce their data for successive periods to terms of calories per square meter per hour and determine the percentage variation of the later values from the basal value. Aub and Means<sup>4</sup>



deal with the total calories per hour and note percentage deviations from the basal total calories. In spite of the variations in point of reference, the percentages so obtained are essentially comparable. In some cases the maximum value obtained is used, in others the value obtained after a definite interval of time. It must be kept in mind, however, that all of these forms of expression deal directly or indirectly with rate of heat production. Such statements to the effect that Patient A has a specific dynamic action of  $x$  per cent, therefore, mean that at a certain period of observation the rate of heat production was  $x$  per cent above the rate in the basal state. The time factor is entirely ignored. Our data have been arranged to show maximum rate of heat production in this manner and are recorded in Table 4 and Charts I to III. Three features require comment: (1) The time of occurrence; (2) the height of maximum rate; (3) secondary maxima.

The patients of the normal and thin groups show the maximum rate of heat production in the first hour, while the apex of the curves for obese group comes in the second hour. The charts show clearly that, although the composite curves follow these trends, the individual curves of each group show great variety, thus precluding any statement of group specificity. Our data in this respect agree with those of Lauter,<sup>21</sup> Kraus and Rettig<sup>20</sup> and others who found marked individual variation in all groups, but a general tendency for the obese to reach the maximum rate somewhat later than the normal persons. Whether the delay is real or merely due to the small number of patients in each series and to the relatively long time between observations is not apparent.

The numerical value of the maximum rate of heat production varies somewhat with the method of calculation and of expression of results. Our observations when arranged in terms of basal metabolic rate and the differences noted in this ratio following the meal are recorded in Table 4. It will be noted that in the first hour the normal group averages 18 per cent increase, the thin group slightly higher, 21 per cent, and the obese group definitely lower, 14 per cent. These data appear to confirm the observations of Mason,<sup>24</sup> Wang, Strouse and Saunders,<sup>36</sup> Plaut<sup>27</sup> and others, that the obese person has a lower and the thin person has a higher percentage increase in rate after food. However, if the data of the second hour are used, the average of the normals has already fallen to 15 per cent, whereas the obese group has risen to its peak of 18 per cent and the thin group remains at 21 per cent. Moreover, there is a rather marked variation among the individual members of each group—normals, 12 to 24 per cent; obese, 13 to 24 per cent; thin 19 to 29 per cent. When the delayed peak of the obese group is, taken into account the similarity of the ranges of variation of the individuals in each group prevents the identification of a group characteristic, a point strongly emphasized by Lauter.<sup>21</sup>

The percentage change in rate of heat production of our series ranges from 12 to 29 per cent. These results are of the same order of magnitude as those for normal persons as determined by other workers.<sup>22,24,27,36</sup> However, attention must be called to the variations in test meals as used by the various observers. Isolated observations of 50 per cent or more elevation have been noted following meals of excessive protein content.

Two factors exert an important artificial influence upon the numerical values of heat effects when expressed as percentage: (1) The numerical value of the base line, and (2) the variations in body surface. The magnitude of the basal value seriously influences the percentage for a given calorie increment. For example: A 10-calorie increase at a 60 calories per hour base line is equivalent to 16 per cent, but at 90 calories per hour the same increment is only 11 per cent of the base line. If it is recalled that grossly obese persons characteristically metabolize at levels 40 to 50 per cent higher than normal persons and thin persons considerably less, the significance of this fact in the calculation of the percentage specific dynamic action data after the manner of Aub and Means for obese, thin and normal persons becomes apparent. The second factor of importance appears in the calculations which use calories per square meter per hour as a basis. This expression requires the division of the total calories per hour by the body surface. Aub and DuBois<sup>3</sup> pointed out that subjects with smaller surfaces have distinctly higher percentage increase after food. A 10-calorie increment in a person with a surface of 1.67 would introduce a variation of 6 calories in terms of calories per square meter per hour and proportionate change in basal metabolic rate expressed as percentage. If, however, the surface is 2.2, as in many obese patients, the apparent variation is 4.5 calories per square meter per hour. Although the caloric increase is constant, an apparent variation is produced if the data are reduced to the described forms. Here again an identical change in rate of heat production produces an apparent depression of percentage of specific dynamic action in the obese and an apparent elevation in the thin. This factor may be minimized by the calculation of the basal metabolic rate and its changes on the basis of ideal weight and surface. The following table records the data for our obese group in the second hour when calculated according to ideal and actual surface.

The basal metabolic rates calculated on ideal weight are higher than upon actual weight, as has been previously discussed.<sup>32</sup> Of more immediate importance, it will be seen that the average specific dynamic rate is increased 4 per cent. This increase is due solely to the use of the divisor, 1.64, the average ideal surface, instead of 2.03, the average observed surface, in dividing the 12.7-calorie increment. Since the numerical value for the ideal surface, 1.64, is quite comparable to that for the normal group, the percentages

for specific dynamic action thus obtained are more essentially comparable to the figures for the percentage specific dynamic action of normals than are the figures based upon actual surface. Our obese patients showed an average of 21 per cent specific dynamic action in the second hour by this calculation as contrasted with 17 per cent by use of the actual surface. Although in our series neither value differs sufficiently from the normal group to be of significance, the point is made that an important fraction of the alleged depressions in specific dynamic action in obesity which have been reported by many authors is due to a mathematical convention rather than to an observation of heat effect.

TABLE 8.—INCREMENT IN METABOLIC RATE CALCULATED ON ACTUAL AND ON IDEAL SURFACES—OBESSE GROUP.

Test.	Total calories.			Area, sq. m.	Actual surface.			Area, sq. m.	Ideal surface.		
	Basal, cal.	Second hour, cal.	Increase, cal.		Metabolic rate.				Metabolic rate.		
					Basal, per cent.	Second hour, per cent.	Increase, per cent.		Basal, per cent.	Second hour, per cent.	Increase, per cent.
1 . . . .	59.9	72.1	12.2	1.63	0.5	21.4	20.9	1.52	7.9	30.0	22.1
7 . . . .	91.2	96.0	4.8	2.42	3.0	8.8	5.8	1.62	54.3	62.4	8.2
24 . . . .	67.6	82.3	14.7	1.99	- 5.7	14.9	20.6	1.62	14.3	39.4	24.9
6*											
12 . . . .	82.5	97.2	14.7	2.06	9.7	29.3	19.6	1.65	37.0	61.4	24.4
14 . . . .	77.7	95.9	18.2	2.04	4.4	28.8	24.4	1.65	29.0	59.2	30.2
25 . . . .	56.1	68.0	11.9	2.03	- 25.2	- 9.5	15.7	1.76	- 13.8	4.4	18.2
Ave. . . .	...	...	12.7	2.03	- 2.2	15.6	17.8	1.64	21.4	42.8	21.4

\* Omitted.

Many patients show a tendency toward secondary and tertiary rises in the heat production curves. The tendency is more pronounced in the normal and thin subjects than in the obese. Three of the normal and all of the thin patients increased their output in the fourth hour with resultant notching of the composite curves. The possibility of an association between these early secondary rises and the fluctuations in response of the gastrointestinal tract to food exists. With regard to the late secondary and tertiary rises, it is our opinion that the reaction is influenced to a large extent by factors quite apart from the test meal. The curves show that 2 of the 5 normals and all 3 of the thin patients failed to return to the basal level of heat production in 8 hours; in fact, 2 of them showed a definite upward tendency at this time. These elevations, we believe, are due rather to the factors of nervous excitement and fatigue resulting from the prolonged confinement of the test which produce an important independent rise in metabolism rather than a delayed influence of the ingested food.

The preceding discussion of the percentage of specific dynamic

action refers to isolated and to average values for maximum rate of heat production. A more proper perspective of the influence of a meal upon heat production requires an appreciation not only of the intensities of reaction but of the durations of those intensities. Lauter,<sup>21</sup> in his analysis, reports his results in terms of calories per 24 hours. He determines the average caloric output for the period of observation and expresses in percentage the variation from the basal calories. Benedict and Carpenter<sup>7</sup> report results in much the same manner, although they select calories per minute as a working unit. The percentage refers, therefore, to the average increase through the observation period. Obviously, the significance of this numerical value is quite different from that of the figures for maximum rate increase. This expression differs from that of maximum rate in that, whereas the former deals with the form of the curve of heat production, the latter is concerned with the area below that curve.

Our data may be presented in a comparable manner. If we assume a constant 8-hour base line it may be noted that in 8 hours the basal calories of the normal group average 466 calories, the obese, 571, and the thin, 449 calories. Since the increments in the respective groups are 51, 58 and 67 calories respectively, the percentage change becomes 11, 10 and 15 per cent respectively. The individual data are recorded in Table 5, Columns 11 and 12. These numerical values bear quite different interrelationships as contrasted to the numerical differences in maximum rate of heat production noted for the respective groups. In fact, it may be stated that no significant variation is apparent in any group.

The figures above described represent the percentage of increase in heat production in 8 hours which might be attributable to the meal in contrast to the percentage of change of rate of heat production which was discussed previously. The statements take into account the entire heat influence of the meal. They are, however, expressions of the ratio of the total caloric increment to the basal caloric output for the corresponding period. It should be noted that, although this method of expressing percentage of specific dynamic action has much more logic to commend it than the statements of maximum rate observation, it is subject to one of the same criticisms, namely, that the numerical value of the ratio is influenced by the size of the basal value. Benedict and Carpenter<sup>7</sup> point out how the total heat effect forms but an insignificant percentage change if the effect of a single meal upon the total heat production for 24 hours is noted. Our normal group, for example, had an average 24-hour basal heat production of 1400 calories. The 51 calories of the meal increased this value by less than 4 per cent. In our above calculations the basal calories for only the period in which the heat influence was manifest is used, that is, 8 hours, the percentage is accordingly 51 calories in 466, or 11 per

cent. Thus, as in the discussion of maximum rate, it may again be seen that identical heat quantities produce dissimilar percentage values at high and low basal levels.

Quite apart, therefore, from the varieties of meaning which may be attached to the term "percentage of specific dynamic action," it is debatable whether this form of expression affords a proper description of the phenomena involved. The use of the percentage values for maximum rates of heat production and for total heat effect may be of help in apportioning the importance of the many factors which contribute to the total 24-hour heat production of a given individual. On the other hand, however, the magnitude of the all-important basal level is affected by a number of factors, such as age, sex, surface, which are independent of and bear no reciprocal relation to the heat produced by standard test meal. Therefore, for the purposes of the comparison of heat effects of a meal in different individuals . . . "The computation of the percentage of the increment is . . . open to serious criticism, and it is difficult to see how such percentages can have real significance." (Benedict and Carpenter.<sup>9</sup>)

*Total Heat Production.* As has been emphasized by Benedict and Carpenter,<sup>7</sup> Lauter,<sup>21</sup> Kraus and Rettig,<sup>20</sup> a true appreciation of the thermal effects of a meal is obtained by focussing the attention upon the total caloric increment which may be observed. Attention must be given not only to the intensity of heat reaction but also to the duration. Given repeated observations of time and intensity, the estimation of the total heat effect is mathematically approximated by the determination of the area beneath a smooth curve drawn through the plotted caloric increments and their respective time factors. The value of such a curve is, of course, dependent upon not only the accuracy of the observations but upon their number. Theoretically, points at 15- to 30-minute intervals are desirable. Practically, 1-hour intervals were feasible. The possibility of the failure of the peak of the production to coincide with an observation time undoubtedly tends to diminish the curve area. However, an appreciable deviation from any observed maximum point would result in a very sharp curve peak which, in consequence, would have only a minimal influence on the total curve area. In spite of the admitted inaccuracies, the area so described gives the best idea of the true effect of the meal on metabolism.

The data which have been detailed above in Table 5 show a heat production of 51 calories and 58 calories for the normal and obese groups respectively. The average deviations of the individual subjects from these means is 7 and 11 in the two groups, or 14 and 19 per cent from the mean. The thin group averages 67 calories with a  $\pm 9$ -caloric deviation, or  $\pm 14$  per cent from the mean. The entire 15 observations average 57 calories  $\pm 17$  per cent. In view of the fact that a deviation of but 1 caloric in the base line

determination produces an 8-calorie, or 14 per cent, deviation in the 8-hour curve, it may be assumed that the error in the determination of total heat effect is on the average no greater than that of the Tissot apparatus alone. The apparently large percentage error is due to the small numerical value of the total heat effect rather than to the technique.

An examination of the curves (Charts I to III) shows a considerable individual variation in each of the three groups. In each group curves of the high type of short duration and the low type of longer duration are represented. The factors producing these individual variations in heat production may in part be related to the natural variations in stomach emptying time as well as to the less demonstrable factors in the digestion and absorption cycles. The close resemblance in the three groups of not only the total area but also the contour of the composite curves is very striking. It may be noted that there is no relation whatsoever between the height of the curve peak and the total area, thus emphasizing the fallacy of confusing maximum rate of heat production with the true specific dynamic action of a meal.

Lauter<sup>21</sup> has criticized in detail the experiments of Plaut and similar work, pointing out the inadequacy of tests lasting 4 hours or less. Again, Kraus and Rettig<sup>20</sup> have shown by Roentgen ray that the average complete emptying of the stomach was  $4\frac{1}{2}$  hours for their test meal. Although Benedict and Carpenter<sup>7</sup> indicated the possibility of an elevation of the basal level in prolonged experiments, our curves suggest that in the 8-hour period we have employed the latter factor is at a minimum. Our data likewise emphasize the protest of Lauter against the use of short experiments. While undoubtedly the principal effect of a meal is manifest in the first 4 hours, approximately one-third of the total heat production occurs in the second 4-hour period.

An examination of the contours of the curves shows delayed secondary and even tertiary rises. These are more conspicuous in the normal and thin groups. The latent rises, as stated above, are perhaps associated with extraneous factors, such as fatigue, which of themselves produce elevations above the basal calories. Benedict and Carpenter<sup>7</sup> have discussed this point at length. An analysis of the hourly heat production data, as shown in Table 5, indicates that in the first half of the experimental period the heat production in all three groups was very closely comparable. In fact, the average figures for 4 hours are normal group, 37; fat, 42, and thin, 43 calories. The major effects of the meal are to be expected in this period, and it is in this period that the observed heat values are practically identical. Much more variation occurs in the second 4 hours. The group figures are 14, 16 and 23 calories respectively. The bulk of the differences in the various groups falls, therefore, in the period of diminished food influence. These facts

support the conception that in the late hours of our tests extraneous influences produce the largest fraction of the difference between the thin and the other groups.

From the above discussion, it may be concluded that the total heat effect of the test meal does not vary significantly in the different groups of subjects. The observed deviations are small and for the most part explicable as resultants of secondary factors. The individual members of each group show a considerable variation in rate of maximum heat production and in time of occurrence of the maximum rate. However, the total heat production is remarkably constant not only in the three groups but in the entire series.

*Thermal Properties of the Meal.* The average value for the extra heat produced by this test meal is 57 calories. This figure is admittedly based upon but 15 determinations. Although the demonstration of the absolute value of the heat effect is dependent upon a much larger series, it is of interest to compare this figure with the data of other authors. Lusk<sup>23</sup> and Kraus and Rettig<sup>20</sup> have shown that 30 per cent of the ingested protein calories are given off as extra heat. Our use of a mixed meal precludes our discussion of pure protein effects, nevertheless, it may be observed that 30 per cent of the 160 protein calories of our meal is 48. Our value for the entire meal, 57 calories, is not inconsistent with the figure suggested by Lusk and Kraus and Rettig. Benedict and Carpenter<sup>7</sup> suggest that the extra heat production from an average meal approximates 13 per cent of the protein calories, 8 per cent of the carbohydrate and 2 per cent of the fat, with an average figure of 6 per cent for the "cost of digestion" of a normal mixed meal. These values when applied to our meal of 40 gm. of protein, 52 gm. of carbohydrate, 26 gm. of fat indicate a heat effect of around 42 calories. The total caloric value of the meal is 610 calories. The 57 calories of extra heat production represent a "cost of digestion" of 9 per cent. This value is somewhat higher than the 6 per cent suggested by Benedict and Carpenter,<sup>7</sup> which may perhaps be explained by the relatively high protein content of this meal.

The problem of the source of the extra heat which is developed has been attacked from many angles. Much discussion has centered around whether protein or carbohydrate alone or in combination provide the extra calories. For the most part, evidence is obtained from the observations of respiratory quotient and nitrogen output. No nitrogen observations were made on this series. However, the data relative to respiratory quotients are quite suggestive. The respiratory quotient figures for the normal and obese groups are recorded in Table 9.

The quotients in the normal series do not differ greatly from those of other authors. There is a definite rise in the respiratory quotient during the first 2 hours accompanying the maximum heat production and a subsequent fall to nearly the initial level. Both protein and

carbohydrate appear to contribute to the extra heat production. In the obese group the average value for the second hour, the time of maximum heat production, is slightly higher than the basal. It is of interest that many of the highest values for respiratory quotients coincide with the peaks of the heat production curves. Even No. 7 shows both the highest respiratory quotient and the apex of heat curve to occur together in the fourth hour. However, in view of the general depression of the respiratory quotient, the failure of any of the average values to reach 0.8 and the practical constancy of the average values during the time of maximum heat production (the first 4 hours), it seems justifiable to suggest that, as far as may be judged from the respiratory quotient, the source of the extra heat is not much different from the source of heat in the basal state. It seems possible that the extra heat is supplied in this event not only by protein and carbohydrate, but that a fair percentage is derived from the combustion of fat.

TABLE 9.—RESPIRATORY QUOTIENTS OBSERVED BEFORE AND AFTER TEST MEAL.

Test.	Basal.	First hour.	Second hour.	Third hour.	Fourth hour.	Sixth hour.	Eighth hour.
<i>Normal.</i>							
2 . . . . .	0.790	0.834	0.760	0.767	0.757		
17 . . . . .	0.825	0.860	0.861	0.839	0.871	0.815	0.811
14 . . . . .	0.780	0.830	0.832	0.828	0.864	0.810	0.820
20 . . . . .	0.848	0.870	0.833	0.825	0.860	0.840	0.839
21 . . . . .	0.770	0.796	0.765	0.762	0.765	0.785	0.808
Ave. . . . .	0.783	0.838	0.810	0.804	0.823	0.812	0.819
<i>Obese.</i>							
1 . . . . .	0.788	0.765	0.802*	0.758	0.713		
7 . . . . .	0.758	0.752	0.738	0.775	0.780*	0.842	0.910
24 . . . . .	0.773	0.756	0.852*	0.768	0.708	0.790	0.823
6 . . . . .	0.698	0.700*	0.689	0.700	0.718	0.678	0.692
12 . . . . .	0.830	0.791	0.807*	0.779	0.773	0.806	0.830
14 . . . . .	0.730	0.723	0.794*	0.780	0.758	0.746	
25 . . . . .	0.720	0.733*	0.721	0.705	0.727	0.706	0.719
Ave. . . . .	0.757	0.746	0.772	0.752	0.740	0.761	0.795

\* Peak of heat curve.

*Unacceptable Determinations.* Of the series of 25 tests 10 have been set aside as unacceptable on technical grounds. These tests illustrated practically all of the discoverable and several unexplained errors in the method. Abnormal base-line variations were discussed above. Five tests were discarded because the base line deviated from the average of the trial basal calories by more than 2 calories. Three were obese and 2 were thin. Four of these patients had apparently been adequately trained, but upon the test morning 1 patient (obese) showed a base line far lower than the average and 4 (2 obese and 2 thin) far higher.



Five tests (1 normal, 4 obese) were discarded because of too great a deviation of the estimated total heat production from the mean of the respective group in spite of the fact that the base lines were apparently satisfactory. In any series of observations made under apparently identical conditions, isolated observations are frequently made which differ widely from the rest of the series. The more complex the proceeding under investigation, the greater does the intrinsic potential variability become. Some relatively simple criterion of admissibility of data is desirable and is provided by general practice.<sup>17</sup> If the deviation of an observation from the mean of the series excluding this value is four times the average deviation of the remaining observations from their mean, the figure may legitimately be excluded as of little practical value. The heat production in these cases varied between 7 and 135 calories, with an average deviation of 48 calories. Three of the 5 gave total heat productions of 28, 11 and 7 calories respectively. The first 2 of these were inadequately trained, with a strong probability of an abnormal elevation of the initial base line. One patient was normal in physique, the other 2 obese. The remaining 2, both obese, gave 135 and 95 calories respectively. No explanation is obvious for these phenomena.

A review of the entire 10 discarded curves shows that there is no tendency for these curves to fall in any single group. The division, furthermore, of the obese into the very high and very low groups is about equal. The average calories per hour for these 10 discards is  $62 \pm 39$  or  $\pm 64$  per cent, as compared with  $57 \pm 10$  or  $\pm 17$  per cent, the average of the accepted tests.

The influence of external temperature upon the specific dynamic action of food has been studied by Rubner.<sup>31</sup> Although our investigations were not primarily concerned with this phenomenon, certain pertinent facts may be recorded. The tests were made at intervals over a period of  $1\frac{1}{2}$  years. With the Tissot apparatus the room temperature does not indicate the temperature of the air breathed, which comes directly from out of doors. Also bed clothing was utilized to the point of maximum comfort of the patient so that the room temperature does not reflect the skin temperature. Successful determinations were made at room temperatures varying from  $18^{\circ}$  to  $27^{\circ}$  C.; average,  $23^{\circ}$  C. None of the abnormal base-line determinations were associated with unusual room temperatures. Of the abnormally low curves, one was done at  $18^{\circ}$ , another at  $24^{\circ}$ , while the high curves were all done above  $23^{\circ}$ —one on a summer day at  $27^{\circ}$  C. One low curve and one high curve done on the same patient 2 days apart had the same room temperature.

It may be stated, therefore, that our experiments do not show any significant influence of room temperature on the determination of heat effect of food as it is usually performed and at the range of temperatures normally encountered in hospital practice.

*Repetitions of Specific Dynamic Action Test on the Same Person.* Specific dynamic action tests were repeated on 3 subjects. Tests 2 and 17 were performed on a normal individual with an interval of 6 months. The first determination unfortunately ran only 4 hours, the last 4 hours being interpolated from a theoretical 8-hour return to base line. The total effect shown on the two curves is 59 and 49 calories respectively, which is as close an agreement as seems possible with the technique.

Three tests, Nos. 12, 14 and 16, were done on the obese patient, who was also an acromegalic, over a period of 5 weeks during which she lost 17 pounds. Two of the tests were technically acceptable, showing 74 and 69 calories respectively, a very satisfactory agreement. The third test was discarded because of a 2.4-calorie deviation of the base line from the average. The calories produced by this patient were the highest found in the obese group. Certain authors report a marked depression in the specific dynamic action of food in the "hypopituitary" type of obesity. It is worthy of emphasis that this patient, who suffered from a well-established pituitary disorder and who was also obese, did not show any evidence of a depressive influence of the pituitary upon the specific dynamic action of food.

Five tests were done on an obese patient over a period of  $1\frac{1}{2}$  years, during which time she lost 151 pounds by dietary methods.<sup>33</sup> Test 7, in March, 1929, and Test 24, in August, 1930, were the only acceptable curves. They showed heat effects of 45 and 55 calories respectively. The weight change between these two tests was 129 pounds. Test 5 was performed upon admission, and unfortunately showed an abnormal base line associated with inadequate training. If this base line might be corrected for the deviation from the probable true basal calories the heat-production curve would become practically identical with that of Test 7. An entirely unexplained phenomenon was associated with Tests 13 and 15, which were performed 3 weeks apart after 3 months of training. Although the base-line deviations in the 2 cases were 1.9 and 1.7 respectively, just within the prescribed limits, the total calories observed were 135 and 22 respectively. A careful review of the technique in both instances has failed to supply evidence as to the cause of either of these deviations. The occurrence of a very high and a very low test between two perfectly normal determinations is noteworthy. It is also of importance that the five curves of this patient show a marked dissimilarity in shape. No. 7 showed a typical slow rising markedly two-humped curve, while No. 24 showed a single high peak in the second hour, with subsequent sharp drop. It may likewise be remarked that the maximum percentage rise in basal metabolic rate in No. 7 was 13 per cent in the fourth hour and in No. 24 21 per cent in the second hour, a difference of 8 per cent. The observed increments in calories per hour at these times were

10.8 and 14.7 calories respectively—a difference of but 4 calories. However, the basal calories were 91 calories per hour, with a surface of 2.42 sq. m. in the first instance, and 67 calories per hour, with 1.99 sq. m. of surface in the second. In the calculations of basal metabolic rate these factors produce an artificial magnification of the numerical difference between the increments in total calories per hour. If the ideal surface is used in the calculations in both instances the values for increase in rate of heat production become 18.3 and 24.9 per cent respectively—a difference of 6 per cent.

Considerable emphasis should be placed upon the variety of response to food obtained in this case. Although this patient and the one preceding were both well trained and coöperative, only two acceptable tests were performed in each case. Variations of the type and magnitude described in both the acceptable and unacceptable classes cannot represent the sudden institution of new or characteristic metabolic phenomena. For example, quite opposite conclusions regarding the influence of weight loss upon specific dynamic action would be drawn from the comparison of Test 7 with Tests 13 and 15, and yet Tests 13 and 15 were performed only 3 weeks apart. This experience suggests caution in the making of deductions from isolated observations.

The results of these repetitions of the specific dynamic action test are in accord with those of Lauter,<sup>21</sup> Means<sup>26</sup> and others who found no appreciable difference in heat effect upon repeated tests in the same individual. Our experience also suggests that there is no constancy of curve type which is characteristic of an individual—far less of a group. The influence of change of weight upon the specific dynamic has been reported by Mason,<sup>25</sup> Rolly<sup>30</sup> and others. When properly weighted our observations exhibit no important alteration of the heat effect of food following a small or a large loss of weight.

Benedict and Carpenter<sup>7</sup> indicate that evidence exists that specific dynamic action may vary with nutritional states and, more especially, it is depressed in starvation. The observations reported on the above patient who was maintained for much of 1½ years on the reduction diet which has been described<sup>33</sup> show that here again no evidence of physiological starvation exists in spite of prolonged adherence to diets of 500 to 700 calories.

**Specific Dynamic Action as a Factor in the Development and Maintenance of Nutritional States.** Among the many factors which have been alleged to be of importance in the development of obesity, a depression of specific dynamic action takes a prominent place.<sup>25,27,36</sup> Not only is it felt that obese persons have a lowered specific dynamic action, but that obese states can be classified into several sub-groupings on the basis of variations of reaction.<sup>27</sup> Von Noorden<sup>35</sup> showed that a daily excess consumption of 200 calories would lead in the course of a year to a deposition of 17 pounds of fat, or 20

pounds of fat tissue. DuBois<sup>12</sup> calculates that an excess of 89 calories per day would add 8 pounds body weight per year. The excessively obese patient probably gains weight at 20 pounds per year or faster, while the milder degrees approach more nearly the lower rate. The caloric excesses, therefore, vary from 90 to 200 calories per day. Benedict and Carpenter<sup>7</sup> state that, on the average in normal people, 6 per cent of a mixed meal is used for its specific dynamic effect. Therefore, on an average caloric intake of 2500 calories per day, 6 per cent, or 150 calories, would approximate the extra specific dynamic heat. The development of obesity within 10 to 15 years on the basis suggested by DuBois would require a real drop in this 150-calorie factor, certainly to 100 or even 75 calories; or, in other words, a 33 to 50 per cent diminution of total heat effect in the mild cases and a total absence of specific dynamic action in the severe grades. Depressions of these magnitudes should be readily demonstrable.

From the data described and discussed above it will be apparent that we have discovered no significant difference in the heat of reaction to food in either mild or severe grades of obesity as compared with normal persons. We are, therefore, in accord with Lauter,<sup>21</sup> who denies an abnormality in specific dynamic action any rôle whatsoever in the initiation of obese states. Furthermore, our group of obese patients included several of the alleged types of obesity. All were found to react in the same manner. It does not, accordingly, seem possible for us to classify various forms of obesity on the basis of variations of specific dynamic action.

Mason<sup>24</sup> believes that an elevation of the specific dynamic action is in part responsible for consistent thin states. Although our data on this point are less numerous than for the obese state, the observed figures indicate rather clearly that no sufficiently large deviation in extra heat production could be present to account for a caloric loss sufficient to explain this state. If the tendency toward greater fatigability in the undernourished during a long experiment is considered, our data show that there is no appreciable difference between the normal and the thin group and far less between obese and thin groups.

The data of this series of patients justify the statement that the development of the various nutritional states is not the result of variations in the quantities of extra heat produced by food in these individuals. These data, however, provide no index of the physiologic response of the subject to this extra heat. It may be noted that in normal persons test meals which utilize 40 gm. of protein cause a rise in basal metabolic rate of 20 per cent within an hour after ingestion. Changes in the rate of heat production of such magnitude necessarily produce abrupt alterations in the existing physiologic status. Although the extra heat quantity which is produced by a fixed meal may be identical in the normal, the obese and

the thin, the physiologic readjustments which are necessitated by this increment are not necessarily the same in the three states.

The physiologic load which is thrown upon the organism by this sudden alteration of the heat production is unique. Many intricate and automatic readjustments are necessitated, especially in the departments of circulation and temperature regulation. Since the reserve capacity of the organism as a whole is always more than adequate to care for any possible rate of heat production if the alteration is gradual, it is obvious that observations of maximum rate of heat production afford no measure of the physiologic strain. The load lies in the abruptness with which the body is called upon to readjust to new levels of heat production. It is, therefore, measured not by the maximum rate of total heat production but by the rate at which the existing rate of heat production is altered.

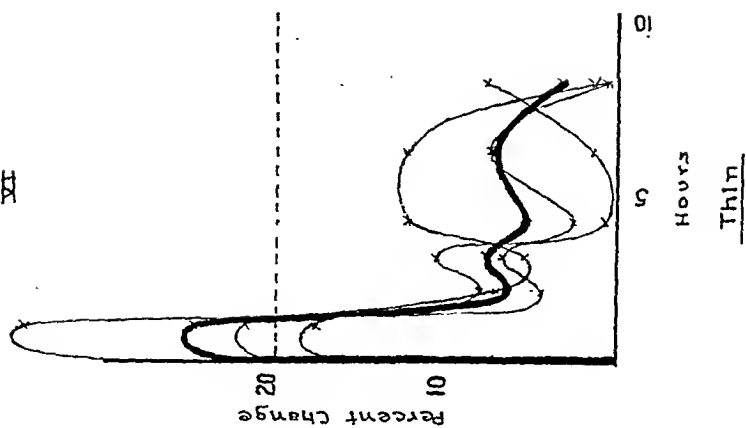
An attempt has been made to obtain a relative numerical measure of the physiologic load which was thrown upon our normal patients by the test meal employed. The basic observations are those of total calories per hour for the successive periods. However, instead of noting the relationship of each observation to the basal determination, the observation is compared with the rate of heat production for the hour immediately preceding. The numerical difference is then divided by the total heat production of the preceding hour in order to give the percentage change, in other words, the rate of change of the rate of heat production. These data have been arranged in Table 9 and plotted in Chart IV.

From the chart it will be seen that immediately following the ingestion of food the curve rises to a sharp peak at the first hour. It is quite probable that the true peak of this curve is obscured by the use of hourly observations rather than those at shorter intervals. For the second and third hours the rate of heat production does not change significantly the low part of these curves corresponding to the nearly flat tops of the curves of rates of heat production (Chart I). The secondary short slow rise with the maximum in the sixth hour represents the period in which the heat effect of the meal is rapidly diminishing and the total metabolism returning to normal. This analysis shows clearly that following a meal the body is required to readjust itself within an hour to a change in heat production of 20 per cent. The subsequent changes are small and comparatively unimportant. The important physiologic strain, therefore, occurs in the latter part of the period of food ingestion and the period immediately succeeding it. Only a small fraction of the total extra heat is produced during this interval, but by the time the maximum rate of heat production has developed, the adaptations to this rate will have been complete. It is, therefore, important to distinguish sharply between the two phenomena which are depicted in Charts I and IV, the rate of extra heat production and the physiologic response to this extra heat respectively.

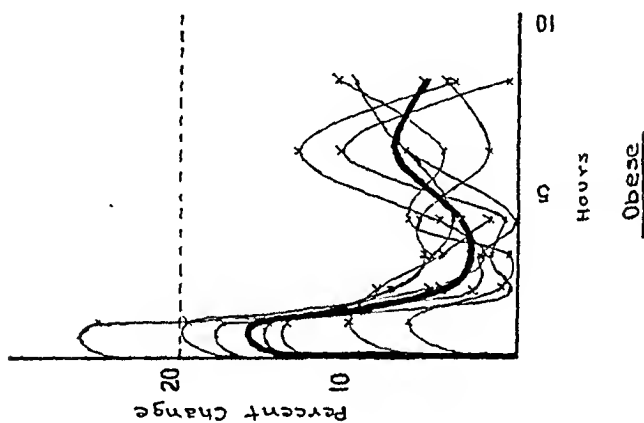
TABLE 10.—RATE OF CHANGE OF RATE OF HEAT PRODUCTION.

Test.	Basal cal.	First hour.			Second hour.			Third hour.			Fourth hour.			Sixth hour.			Eighth hour.		
		Cal.	Diff.	Per cent.	Cal.	Diff.	Per cent.	Cal.	Diff.	Per cent.	Cal.	Diff.	Per cent.	Cal.	Diff.	Per cent.	Cal.	Diff.	Per cent.
2 . .	57.0	71.9	14.9	26.1	68.9	3.0	4.1	67.5	1.4	2.0	65.1	2.4	3.7	56.6	3.1	5.1	52.6	4.0	7.0
17 . .	54.1	66.0	11.9	22.0	65.2	0.8	1.2	63.0	2.2	3.4	59.7	3.3	5.2	56.0	8.3	10.8	69.2	0.2	0.3
4 . .	70.4	84.9	14.5	20.5	77.8	7.1	8.3	78.9	1.1	1.3	77.3	1.6	2.0	69.0	2.9	4.8	55.8	1.6	2.8
20 . .	51.1	60.2	9.1	17.8	59.1	1.1	1.8	60.9	1.8	2.1	60.3	0.6	0.9	57.4	0.9	1.4	63.4	1.4	2.2
21 . .	58.6	66.5	7.9	13.5	65.3	1.2	1.8	66.0	0.7	1.0	62.9	3.1	4.7	62.0	...	5.5	...	...	3.1
Ave.	...	...	...	20.1	...	...	2.4	...	...	2.0	...	...	3.3	...	...	...	...	...	...
1 . .	59.9	66.6	6.7	10.0	72.1	5.5	8.2	69.0	3.1	4.3	67.8	1.2	1.7	...	...	...	...	...	...
7 . .	91.2	97.0	5.8	6.3	96.0	1.0	1.0	95.5	0.5	0.5	102.0	6.5	6.5	97.5	4.5	4.4	87.0	10.5	10.7
24 . .	67.6	77.0	9.4	13.9	82.3	5.3	7.5	77.8	4.5	5.5	73.3	4.5	5.9	72.0	1.3	1.7	69.0	3.0	4.1
6 . .	64.8	77.5	12.7	19.6	73.5	4.0	5.1	75.0	1.5	2.0	71.5	3.5	4.7	62.2	9.3	13.0	59.8	2.4	3.9
12 . .	82.5	97.0	14.5	17.5	97.2	0.2	0.2	95.5	1.7	1.7	94.6	0.9	0.9	84.6	10.0	10.5	85.1	0.5	0.6
14 . .	77.7	89.3	11.6	14.9	95.9	6.6	7.4	91.6	4.3	4.3	88.0	3.6	3.9	82.1	5.9	6.7	...	...	...
25 . .	56.1	70.0	13.9	24.8	68.0	2.0	2.8	66.5	1.5	2.2	66.5	0.0	0.0	62.0	4.5	6.7	56.0	6.0	9.6
Ave.	...	...	...	15.3	...	...	4.6	...	...	2.9	...	...	3.3	...	...	7.1	...	...	5.7
9 . .	60.2	70.8	10.6	17.6	76.5	5.7	8.0	68.4	8.1	10.6	67.9	0.5	0.7	67.0	0.9	1.3	61.9	5.1	7.6
11 . .	60.6	73.9	13.3	21.9	68.7	5.2	7.0	65.0	3.7	5.3	72.9	7.9	12.1	64.0	8.9	12.2	63.6	0.4	0.6
23 . .	47.4	63.8	16.4	34.6	61.0	2.8	4.3	56.9	4.1	6.7	58.5	1.6	2.6	54.1	4.4	7.4	54.8	0.7	1.2
Ave.	...	...	...	24.7	...	...	6.4	...	...	7.5	...	...	5.1	...	...	7.0	...	...	3.1

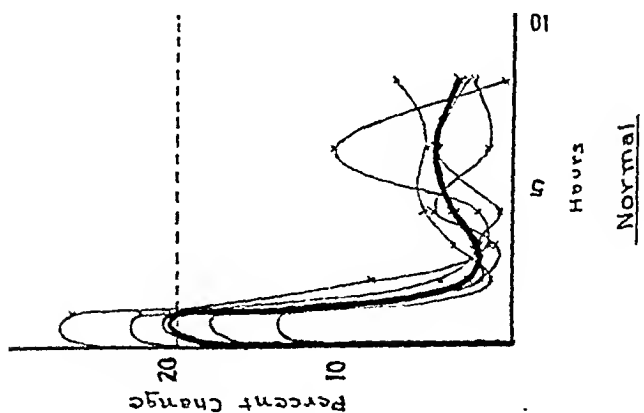
IX



V



XII



CHARTS IV TO VI.—Rate of change of rate of heat production.

If now the physiologic load which is thrown upon the obese and upon the thin by the specific dynamic action of food is approximated in the manner described above rather important variations are revealed. Table 9 and Chart V indicate the rate of change of heat production in the obese group. The general form of the curve is quite comparable to that of the normal group. The significant point is that the maximum of the composite curve falls at 15 per cent, which is 25 per cent less than for the normal group. On the other hand, the thin group as shown in Chart VI reaches its maximum at 25 per cent, which is 25 per cent higher than the normal group. It will thus be seen that although identical meals produce the same total heat of reaction in normal, thin and obese persons, the physiologic load which this extra heat production throws upon the body is approximately one-fourth less in the obese and one-fourth greater in the thin than in the normal. In fact, the thin group bears a 66 per cent greater physiologic strain than the obese in the handling of a meal which is identical in protein, fat and carbohydrate, but particularly in total calories.

The above data bring out the fact that the great difference between the various nutritional states lies, not in the total extra heat production from food, but in the differences in physiologic load which are thrown upon the organism. If it were possible to demonstrate a relationship between this physiologic load and the sensation of satiety which normally determines the limit of food ingestion, an important factor would be exhibited in the chain of causes which determine why fat people unwittingly eat large meals and stay fat and thin people automatically eat small meals and remain thin.

The analysis of a possible relationship between satiety and the physiologic stress resulting from the specific dynamic action of food is difficult and will be reserved for a later discussion. If this relationship may be assumed, it is probable that when the existing rate of heat-production changes at a certain rate, for example, 15 per cent per hour, the body as a whole experiences a feeling of comfort and wellbeing, but when the rate of change is appreciably increased, for example, to 20 per cent per hour, the body rebels against the load and automatically prevents further insult by preventing further food intake—that is, complete satiety. As a corollary of this hypothesis, it follows that when the total metabolism is low a person on general diet will be satisfied by a smaller food intake with its smaller specific dynamic action and total calories than when the total metabolism is high. The normal individual leading a routine existence has a relatively stereotyped curve of variation of heat production throughout the day, with a resultant constant total output. It thus becomes obvious that with the same level of total heat production at corresponding meal times each day a person on a general mixed diet would tend not only to reproduce the same



specific dynamic action with its same resultant physiologic load, but also to repeat the same total caloric intake. It seems reasonable to assume that some such physiologic mechanism is responsible for the well-known fixity of individual eating habits which, in turn, is responsible for the equally astonishing relative fixity of body weight.

From this point of view, the etiology and persistence of abnormal nutritional states becomes more understandable. In the discussion of satiety in normal persons it was assumed that the optimum feeling of wellbeing paralleled a rate of change of heat production of 15 per cent, and that when this rate increased to 20 per cent a feeling of absolute satiety ensued which prevented further food intake. By the application of these same figures to the curves of the thin and obese groups a striking observation will be noted at once. Whereas in the normal persons the satiety point, 20 per cent, corresponds to the peak of the heat curve, in the thin the satiety point was passed long before the peak was reached. This may be interpreted to indicate that the test meal was considerably greater in specific dynamic action and, therefore, in total calories than a meal which these persons would voluntarily have selected. On the other hand, the peak of the obese curve fails to reach the satiety level by 25 per cent, and, in fact, coincides with the level of optimum sensation. A comparable interpretation of this fact would suggest that the test meal, with its fixed total calories and specific dynamic action, would quite fail to satisfy these patients. In other words, if we assume that the test meal, with its 40 gm. of protein and 610 calories, completely satisfied the normal group, the thin patients, if permitted free selection of food, would have been satisfied with much less food, whereas the obese group would require a far greater intake. The selection of the values, 15 and 20 per cent, for the critical points is quite arbitrary, and more careful investigation may reveal entirely different true levels. However, regardless of the levels selected, the fundamental difference between the three groups will persist. Furthermore, it may later be shown that the peaks of the curves of rate of change of heat production fall earlier in the thin group and later in the obese group than in the normal group. If, for example, the peaks were found to be at 20 minutes 40 minutes and 60 minutes in the thin, normal and obese groups the resultant effects upon their relative total food intakes would be accentuations of tendencies described above.

It will, therefore, be seen that the same factors which operate to produce the fixed eating habits and fixed body weights of normal individuals may become perverted in two directions. The resultant extreme in one case is the apparently healthy person who persistently holds a weight 20 to 25 per cent below normal. He functions at a low metabolic level<sup>10</sup> and receives his optimal specific dynamic action stimulus from a small food intake which maintains his weight

by a caloric intake equivalent to his output. The other extreme is the likewise apparently healthy person who maintains a weight 50 to 200 per cent above normal. This person operates at a very high level.<sup>32</sup> He holds his weight, or, as usually happens, slightly increases his weight, because of the correspondingly large caloric intake which is required to produce the requisite rate of change of heat production for optimum sensation. The persistent small intake of the thin and large intake of the obese are probably further aggravated by secondary phenomena both psychic and mechanical. In both of these abnormal states vicious habit cycles are firmly established. It may be emphasized that in neither case does any new pathologic factor in metabolism exist. The thin person stays thin because at his low metabolic level the food intake which produces a specific dynamic action giving him the optimum sensation of comfort amounts to 1500 to 1800 calories. The fat person stays fat because at his high metabolic level a 3000 to 3500 caloric intake is required to give him the same optimum sensation.

If the fundamental abnormality in extreme nutritional states is associated with the metabolic phenomena described above and with the resultant vicious habit cycles, it, therefore, seems possible to correct either of these states by breaking up these vicious cycles. This can be done by dietary procedures. In practice it is a relatively simple matter to take weight from an obese person, but, as a rule, less easy to fatten a thin one. The obvious explanation is that the obese person receives an adequate, though perhaps not optimal specific dynamic action stimulus, three times a day by a maintenance protein diet.<sup>34</sup> This diet is high in protein, with its intense specific dynamic action, but low in both carbohydrate and fat and, therefore, very low in calories. The large caloric deficit thus secured produces rapid weight loss but with comfort. The thin patient, however, presents a much more difficult problem because an alteration in diet produces, not a mere absence of pleasurable sensation as in the obese, but a positive discomfort which frequently amounts to pain and in which the secondary psychic and mechanical factors are also of great significance. The sensations involved in the adherence to a diet 1500 to 2000 calories below maintenance are far less distressing than those which accompany a diet 1500 to 2000 above maintenance. In consequence, persistence and patience are required on the part of the thin person to endure the distress which is caused by the specific dynamic action of a diet containing sufficient additional calories to secure weight gain. A 3500-calorie diet with its total specific dynamic action of approximately 200 calories produces an optimum sense of wellbeing in a fat person but an acute distress in the very thin. In either case, as the weight becomes normal, a reëducation of the sensorium and the establishment of new eating habits is a relatively easy matter.

The suggestion is, therefore, made that specific dynamic action

of food does have an influence upon the development of abnormal nutritional states. This effect is not direct nor is it due to a quantitative difference in the heat of reaction to food. Indirectly, however, the rate of change of heat production which is caused by the heat of reaction to food may be reflected in sensations such as satiety and thus influence the amount and type of food intake which, in turn, are the principal factors productive of weight changes.

**Conclusions.** 1. The total heat effect of a meal throughout the period of production of this extra heat is the logical basis for comparison of the heat effects of food in different individuals and bears no relation to the maximum rate of heat production.

2. Evidence is described showing that the heat of reaction or "cost of digestion" of a given fixed meal is the same regardless of the state of nutrition of the subject.

3. If the specific dynamic action of food may be related to the development and maintenance of abnormal states of nutrition, it is through the different degrees of satiety produced by the same increase in total heat production which accompany these states and which, in turn may be regulators of both quality and quantity of food intake.

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## EXTRA-POLLEN HYPERSENSITIVITY—AN IMPORTANT CONSIDERATION IN THE TREATMENT OF HAY FEVER.

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THE treatment of hay fever remains, essentially the same today, as when the principles thereof were first laid down by Blackley<sup>1</sup> in describing and performing the cutaneous test and since their first practical application in England by Noon and Freeman<sup>2</sup> in 1911, and later by Clowes,<sup>3</sup> Koessler<sup>4</sup> and Cooke<sup>5</sup> in this country:

The experience of years has increased our information concerning many phases of the subject. The fundamental problem is that which deals with ways and means of bringing about 100 per cent successful therapeutic results.

As is generally known, the results in hay fever treatment have been poor in the hands of the profession at large, who as a rule make use of the commercial preparations on the market. Many explanations have been offered to account for this. "Because of the limited number of reagents utilized for accurate diagnosis and because of the limited time available for the entailed study of hay fever patients, the indiscriminate use of pollen extracts and employment of shotgun preparations have followed as a matter of course and have been responsible for disappointments."<sup>6</sup>

Yet "even in the hands of men well trained in this specialty, there exists a constant marginal percentage of failures."<sup>7</sup> Hence maxims and rules have been laid down for the purpose of minimizing unsuccessful results. It has been urged to follow strictly the following requisites if one is to obtain the best therapeutic results."<sup>7</sup> (1) Correct diagnosis; (2) Proper treatment by individualization of dosage, or "optimal" dosage. Raekeman<sup>8</sup> believes that success in the treatment demands a course of doses of a size and extent which is optimal for the particular patient; (3) Storage in concentrated form and refrigeration to preserve the potency of the pollen. (4) Pre-seasonal combined with co-seasonal treatment. (5) Avoidance of overtreatment. Does the adherence to the above principles help eradicate the marginal failure? Not so, not even in the best of hands and under closest adherence to the most modern and scientific ideas on the subject as thus far set forth. The question arises, what have we overlooked? May there not be one other factor entirely left out from consideration by most writers, which if properly understood and applied may solve our therapeutic problem? The author is convinced that there exists such a factor.

Many writers had hitherto stated that many seasonal hay fever subjects are also sensitive to substances other than pollen, such as epidermals or foods. They recorded the observation that the offending agents in question tend to make the hay fever worse during the season.

Among the earlier writers on the subject who recognized the necessity of checking up for all types of allergens may be mentioned Eycrman,<sup>9</sup> Balyeat<sup>10</sup> and Kern.<sup>11</sup>

Balyeat made a study of 719 cases of hay fever and found pollen as the sole reactor in only 52.1 per cent.

Kern's discussion on the subject of the "Causes of Failure in Hay Fever Treatment," is very enlightening and proves how some have clearly recognized extra-pollen sensitivity as a major cause in the failure in hay fever treatment. I quote from Kern's article.

"The question might be put, If a hay fever patient is sensitive also to goose feathers why does he have symptoms only in the pollen season? Why do his symptoms not continue throughout the year? The answer is not certain, but this seems a plausible explanation. A patient may be strongly sensitive to ragweed and only very slightly

so to goose feathers. The feather sensitivity is so slight that his mucous membrane in a normal state is not vulnerable but only becomes so when inflamed and therefore more permeable as a result of the more intense pollinosis. Consequently, in the pollen season, the feather sensitivity may succeed in aggravating the disease, and if unrecognized, bring about the failure in pollen treatment." Moreover, recently workers in this field have begun to show renewed interest in these extra-pollen irritants. Thus Rowe<sup>12</sup> concludes in a recent article: "The allergist must study the patient complaining of seasonal hay fever from the point of view of sensitization to other than pollen allergens."

Fosket<sup>13</sup> mentions the importance of checking up for reactions to substances other than pollen in cases in which the routine pollen treatment proves unsatisfactory. Cohen and Rudolph<sup>14</sup> summarize the subject matter clearly and concisely by stating:

"Sometimes there is a coexisting sensitivity to some substances other than pollen which may exacerbate the symptoms during the hay fever season. Further consideration of this point led us to the belief that failure to discover and eliminate these extra factors has been responsible for the majority of failures to obtain relief by specific methods."

In 1929 I wrote: "In a number of cases carefully chosen, showing not any or partial relief, a study of extra-pollen sensitivity was undertaken for the purpose of determining whether or not that might be taken to account for the nonresponse to the treatment. For comparative purposes, the results of such sensitization tests in a parallel series of patients who obtained excellent results from the pollen treatment are also tabulated. The results seem to warrant the conclusion that extra-pollen hypersensitivity may be given as a factor which when present to a marked degree precludes the possibility for complete and successful desensitization in seasonal hay fever treatment." It is my purpose to show herein from the case reports that follow that extra-pollen hypersensitivity is a most important consideration in the treatment of hay fever.

**Case Reports.** CASE I.—S. H. S., female, aged forty-two years, has been having hay fever for the last eighteen years. She was found sensitive to the ragweed pollens and to plantain. She has been receiving treatments for the past two seasons.

She is intelligent and very coöperative and is greatly interested in her own problem, and shows marked aptitude in understanding all of the complications that surround her malady. She was tested routinely for the pollens as well as for a great number of the inhalant and food proteins by the intradermal method. She was given a list of instructions as to what contacts to avoid and what not to eat.

The very interesting observation had been made by herself, that the slightest contact with dust during the hay fever season immediately predisposed her to the severest seizure of hay fever symptoms. She is careful to avoid that particular offending agent. I made it a point to give her inoculations of dust extract in ascending dosage along with her pollen

treatments and as part of the therapeutic measure during the hay fever season. She appeared very happy one day in September, 1930, when she gladly advanced the information that she was greatly relieved to know that her agonies of eighteen years' duration had finally ended. Strict avoidance of dust and daily injections of small quantities of dust extract (up to 0.3 cc.), then a gradual increase in dosage, and given twice a week, brought about subsidence of symptoms.

She consented to volunteer herself for the purpose of determining whether or not contact at will with particular inhalant proteins, or ingestion of certain food proteins, can actually bring on spells of hay fever symptoms. Since she showed a sensitivity of 5+ to corn, it was decided to allow her to eat her favorite dish once at supper. Symptoms developed, which lasted throughout the night and the following day.

As long as this patient was receiving dust extract inoculations at regular intervals during the hay fever season along with her pollen extract treatments she was in excellent condition. Just as soon, however, as the dust extract was at one time or another left out of her treatment menu she would be seized by hay fever symptoms.

CASE II.—N. K., aged thirty-five years, a janitor in a church by occupation, has had hay fever for the past six years. Up to this year, and for the last three years, he has been receiving treatments regularly pre-seasonally and co-seasonally. The results from the treatment, however, had been persistently poor. This time, in 1930, it was determined, for the first time, that he was sensitive to many inhalants and a few food substances, in addition to the ragweed pollens. He was cautioned against these offending agents. One of the principal reactors was stock dust, and skin reaction to the intradermal test was repeatedly 4+.

He received a thorough course of pre-seasonal treatment which I was planning to continue during the season. Nevertheless, as the late hay fever season set in the results were disappointing.

I was greatly puzzled to find that even on Sundays he would react miserably with marked hay fever symptoms. I reasoned that it could not be the dust he was in contact with, in spite of the precautions which he assured me he was taking. The inoculation of dust extract given him should have protected him. The fact, too, that Sundays brought no relief, excluded dust from consideration as an extra factor. I could not, moreover, understand why his report always included Saturday as a day when he was absolutely free from hay fever symptoms. Finally, it was discovered that the patient was a Seventh Day Adventist, and therefore rested at home, away from his usual occupation, on the Sabbath, or Saturday. It was arranged that he obtain a four-week change of occupation; his symptoms cleared up.

CASE III.—Miss M. H., aged thirty-five years, has been suffering from late hay fever for two seasons. She was under my care last year, with good results. She was found sensitive to many food substances. The two principal reactors were beef, 4+, and pork, 5+. On Columbus day, 1930, she invited guests for breakfast. She fried bacon and partook of it liberally. She was soon seized with severe hay fever symptoms.

CASE IV.—H. R., aged thirty-eight years, a physician, was found sensitive to the tree pollens. His principal reaction was to red oak. Proper treatment definitely controlled his hay fever symptoms. He is emphatic in his statement that just as soon as he eats no more than one cherry during the tree hay fever season he is immediately seized by most violent hay fever; he is otherwise free from symptoms.

(The above case was called to my attention by Dr. M. M. Peshkin, of New York.)

*Comment.* Many other case reports could be cited to illustrate the presence of extra-pollen factors as irritants during the hay fever season, to the extent that they tend to make the hay fever worse and are responsible for the failure in treatment. Only outstanding reports are given here in order not to burden the reader with uninteresting material. Although the most common inhalant substances found to complicate the sensitivity of many of our patients were dust, orris and animal epithelia, yet our case records include the presence of sensitivity to representatives of each group of the inhalant and food series to an equal and as marked a degree.

I found particularly that with the inhalant allergens, it was not sufficient simply to eliminate contact but also to institute actual treatment against such agents as dust or orris, both pre-seasonally and co-seasonally.

With the food substances as complicating factors, elimination of contact or avoidance of ingestion of the particular irritant factor was sufficient to help toward successful results in the hay fever treatment.

**Summary.** 1. Our knowledge and information concerning the treatment of hay fever has in recent years increased greatly indeed. The outstanding problems have always been directed toward bringing about absolute therapeutic results.

2. The results in hay fever treatment in the hands of the profession at large are generally markedly disappointing. Reasons are cited to explain this.

3. Even in the hands of men well trained in the treatment of hay fever, there exists a marginal percentage of failure.

4. Extra-pollen hypersensitivity may be the cause of such a marginal percentage of failure.

5. In the present study, case reports are presented that tend to show that extra-pollen hypersensitivity is a most important consideration in the treatment of hay fever.

6. Desensitization was found necessary both pre-seasonally and co-seasonally against the inhalant allergens. With foods as complicating factors, avoidance of ingestion during the season was found sufficient.

**Conclusion.** Extra-pollen hypersensitivity should receive serious consideration when treating patients for seasonal hay fever. All such patients should be tested routinely with the inhalant and food allergens. When found sensitive to the inhalant proteins they should receive desensitization both pre-seasonally and co-seasonally. When found sensitive to foods, these should be eliminated from their diet during the season.

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## APPENDICITIS IN CHILDREN.

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THE problem of appendicitis in infants and young children is quite different from that in adults. In the first place, especially in infants, a satisfactory history is often difficult to obtain. Parents are prone to overemphasize unimportant events and will very often fail to recall the more important features of an illness. Second, physical examinations on the very young are difficult to do and the findings hard to interpret. The child is sick and often very irritable; besides he is often away from home among strangers and frightened. An infinite amount of patience and time is required before coöperation can be obtained. Differentiation between voluntary and involuntary muscle spasm is often impossible, localization of the maximum point of tenderness is difficult, rectal examination is often unsatisfactory or impossible, and, finally, chest pathology may be hard to rule out. Because of these factors children more than adults consult a doctor late in the disease. Even with the best of coöperation the physician may have a difficult time differentiating the trouble from acute pyelitis, upper respiratory infections, pneumonia, urinary calculi and the ordinary gastrointestinal upsets.

On the other hand, occasionally a diagnosis of acute appendicitis is made in very young infants when the actual condition is a primary peritonitis.

The following report is based on the records of 111 consecutive appendectomies performed on children at the University Hospital, from January, 1920, to January, 1929. All of the children were under 13 years of age. During this same period of time there were in all 700 primary appendectomies performed. Children under 13 years made up 15.8 per cent of all these cases; only 2.6 per cent of these were in children under 5 years of age. Table 1 shows the proportion of children to adults by various authors for different age groups:

TABLE 1.—DISTRIBUTION OF CASES ACCORDING TO AGE.

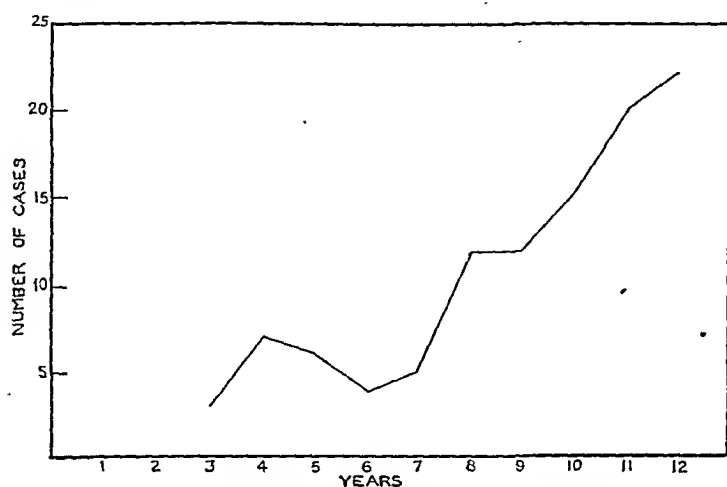
Author.	Number of cases.	Maximum age.	Per cent.
McCosh <sup>1</sup> . . . . .	1000	15	8.50
McCosh . . . . .	1000	5	1.70
McCosh . . . . .	1000	3	0.40
Bellington <sup>2</sup> . . . . .	742	15	22.00
Hoffmann <sup>3</sup> . . . . .	2560	4	0.82
Riedel <sup>4</sup> . . . . .	1222	15	6.70
Fowler <sup>5</sup> . . . . .	..	..	16.40
Churchman <sup>6</sup> . . . . .	1223	5	0.73
Churchman . . . . .	1223	15	16.00
Eliason <sup>7</sup> . . . . .	..	10	9.40
Eliason . . . . .	..	5	2.70

**Age.** The youngest patient was a girl, aged 2 years and 7 months. The next youngest was a boy aged 2 years and 10 months. Both had acute suppurative appendicitis and 1 was complicated by a diffuse peritonitis. Both recovered. Appendicitis in the very young is relatively uncommon. The youngest reported case is that of Coreoran,<sup>8</sup> who reviewed an autopsy on a child 2 days old, in which he found the appendix perforated and believed that this had occurred during prenatal life. Jackson<sup>9</sup> reported another autopsy on a child 40 hours old, who died of mercurial poisoning, whose appendix showed signs of congestion with firm adhesions, binding it down to the neighboring organs. Dixon<sup>10</sup> also reported a case in a premature child 24 days old. Kermisson<sup>11</sup> had a case 11 months old and was able to find records on only 11 other cases near this same age. Abt<sup>12</sup> collected 80 cases under 2 years of age, with a mortality of 50 per cent.

Sixteen per cent of the children in this series were under 5 years of age. Beth reported 20 per cent. Fig. 1 demonstrates the marked increase in the number of cases with each year of life after 7 years; from the age of 2 to 7 years the cases seem to be distributed at a low and almost even rate.

**Sex.** According to the table of collected cases, most authors have found a predominance of male cases over female. Our figures show almost equal distribution, with 54 per cent females and 46

per cent males. There is no adequate reason why in children one sex should be represented by more cases than the other. In adults, as in children, there was a slight increase in the number of females in the interval and subacute cases, while in the acute cases there was a preponderance of males.



APPENDICITIS IN CHILDREN—ACCORDING TO AGE

FIGURE I

TABLE 2.—DISTRIBUTION OF APPENDICITIS IN CHILDREN ACCORDING TO SEX.

Author.	Date.	Cases.	Age limit.	Males, per cent.	Females, per cent.
Erdmann <sup>14</sup>	1907	60	..	59	41
Beth <sup>15</sup>	1908	100	12	52	48
Deaver, H. C. <sup>16</sup>	1910	500	15	63	37
Fowler <sup>5</sup>	1912	183	12	63	37
Porter <sup>16</sup>	1918	100	15	48	52
Alexander <sup>17</sup>	1920	500	15	57	43
Beekman <sup>18</sup>	1924	145	..	63	37
Edberg <sup>19</sup>	1926	754	15	52	48
Seeger <sup>20</sup>	1926	61	..	67	33
Farr <sup>21</sup>	1928	889	..	50	50
Peterson <sup>22</sup>	1929	100	6	71	29
Holt <sup>23</sup>	..	101	..	72	28
Richter <sup>21</sup>	..	185	..	60	40
Total		3678		60	40

**Seasonal Incidence.** The highest number of cases occurred during the fall, with summer ranking second. Alexander<sup>17</sup> found the incidence in children highest in the summer time. There was also noted a definite tendency for the cases to appear in epidemic form.

**Infections.** Whether or not acute respiratory infections, contagious diseases and gastrointestinal disorders precipitate attacks of acute appendicitis is difficult to prove. Thirteen per cent of

our cases gave a definite history of some recent previous acute infection. Especially prominent were the upper respiratory diseases. There was also 1 case each of measles, whooping cough and scarlet fever. Porter<sup>16</sup> reports as high as 60 per cent previous sore throats and tonsillitis; Richter,<sup>24</sup> 4.06 per cent acute infections, with the presence of some sort of focal infection in 24.4 per cent. Brenne-  
mann<sup>22</sup> reports 17 per cent sore throats in 35 cases in hospital practice, while in 10 private cases 9 had an accompanying pharyngitis or tonsillitis. Reiche<sup>26</sup> found 19 cases of acute appendicitis among 7015 cases of diphtheria.

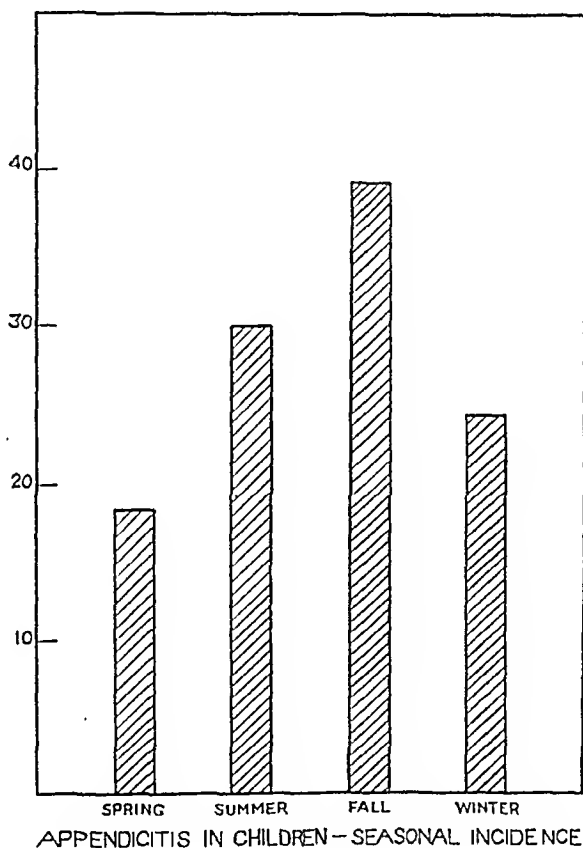


FIGURE II

It must be continually borne in mind that cases with tonsillitis can give symptoms very suggestive of appendiceal infection. Pneumonia, especially of the right lower lobe, is very often mistaken for appendicitis. Several cases were admitted to the hospital with the latter diagnosis which was ruled out only by careful history taking and by thorough chest and abdominal examinations. Roentgen ray examination in such patients may be very helpful. Patients with pneumonia usually appear sicker than those with appendicitis and often have flushed cheeks, dilating alae and rapid shallow respirations. The temperature, pulse and leukocyte count are

generally higher in pneumonia also. Berger<sup>27</sup> found that in 145 cases of pneumonia in children, seen at the Boston City Hospital, from the age of 2 to 15 years, 25, or 17 per cent, were originally admitted with the diagnosis of acute appendicitis.

**Previous Attacks.** There was a definite history of previous attacks in 35, or 31 per cent, of our cases. This is higher than any report listed in the table below, probably because of the fairly large number of interval cases seen at the University Hospital.

TABLE 3.—PERCENTAGE OF PREVIOUS ATTACKS.

Author.	Age limit.	Cases.	Per cent.
Helmholz <sup>28</sup> . . . . .	5	15	6
Helmholz . . . . .	15	53	30
Mitchell <sup>29</sup> . . . . .	12	40	6
Fowler <sup>5</sup> . . . . .	12	183	11
Richter <sup>24</sup> . . . . .	12	172	22
Gray <sup>30</sup> . . . . .	12	200	5
Bolling <sup>31</sup> . . . . .	15	123	12

**Classification of Cases.** The most satisfactory grouping of cases was found to be the surgicopathologic. The cases were divided into the following groups:

1. Interval appendicitis.
2. Acute suppurative appendicitis.
3. Acute suppurative appendicitis with local peritonitis.
4. Acute suppurative appendicitis with abscess.
5. Acute suppurative appendicitis with diffuse peritonitis.

Each type will be discussed separately and will include clinical and microscopic findings. Each case was classified clinically under one of the following headings: (1) Mild, (2) moderate, (3) severe and (4) moribund.

Every appendix removed was examined both grossly and microscopically by the hospital pathologist and classified under one of the following three headings: (1) Acute recurrent appendicitis (evidence of previous infection manifested by scarring or with the presence of perivascular round-cell infiltration in the serosa); (2) acute suppurative appendicitis; (3) no evidence of inflammation.

1. *Interval Appendicitis.* There were 29 cases in this group. In nearly every record there was a history of one or more previous attacks of rightsided pain accompanied by anorexia, nausea or vomiting. A few cases were doubtful and might possibly be classed as chronic appendicitis. They were explored after thorough study had been made and every other diagnostic possibility had been ruled out. There were also included some cases of subacute appendicitis and some of subsiding acute appendicitis. There were no deaths in this group. Clinically all of the cases appeared mild. Microscopic examination revealed acute recurrent appendicitis in 9 cases, suppuration in 2 and no inflammation in 18. The average leukocyte count was 10,000 and the average polymorphonuclear percentage was 69. The majority of these patients had normal

temperatures, with only 5 over 101° F. The pulse corresponded closely to the temperature.

2. *Acute Suppurative Appendicitis.* This group included 13 cases and was made up of those that showed only suppuration of the appendix with no secondary involvement elsewhere. There were no deaths in this group. Clinically, 3 cases were considered mild, 8 moderately severe and 2 severe. Microscopically, 10 appendices showed supuration; in 3 there was only slight evidence of inflammation. The average leukocyte count was 13,000, with an average polymorphonuclear percentage of 84. In two-thirds of the cases the temperature was normal. In no case was it over 103° F. The pulse rate corresponded fairly accurately with the temperature.

3. *Acute Suppurative Appendicitis with Local Peritonitis.* There were 25 cases in this group, with 1 death. The average leukocyte count was 17,000, with an average polymorphonuclear count of 83 per cent. Seventeen cases were considered moderate in severity and 7 severe. Only 1 was considered mild. All of the appendices showed suppuration microscopically. Eleven cases had an elevation in temperature of 101° to 102° F., but no higher. The pulse rate ran parallel to the temperature.

4. *Acute Suppurative Appendicitis with Abscess Formation.* This group included 33 cases, the largest number for any single class. Besides the abscesses localized around the appendix, there were included those more remotely situated, such as the pelvic, subdiaphragmatic, subhepatic and those in the flank. There were 3 deaths in this group. The average white blood count was 21,000, with an average polymorphonuclear count of 88 per cent. Only 1 case presented mild symptoms, 12 were considered moderately severe, 17 severe and 3 were classed as very severe or moribund. All specimens removed showed evidence of suppuration microscopically. In 1 case the abscess was drained, leaving the appendix in for later removal. Thirteen patients had temperatures of 100° F. or less, while 9 had a fever of 102° to 103° F. The pulse rate was higher in more cases than was the temperature, especially in the more seriously sick children.

5. *Acute Suppurative Appendicitis with Diffuse Peritonitis.* Fortunately there were only 11 cases in this group, as it has the highest mortality rate—3 deaths, or 28 per cent. All of the cases had diffuse peritonitis of appendiceal origin. All were considered as seriously sick children on admission. All of the appendices removed showed suppuration. The average leukocyte count was 21,000, with 81 per cent polymorphonuclears. The temperature in all was 100° F. or more; 5 were 103° F. or over. The pulse rates were elevated, but in only 2 cases was it markedly increased. Operation was performed in each case, the appendix removed and the abdomen adequately drained with numerous soft rubber tissue drains of the Penrose type.

**Urine Examination.** Nineteen per cent of the cases showed abnormal urinary findings. None of these were operated upon until urinary disease had been satisfactorily ruled out.

TABLE 4.—URINE EXAMINATIONS.

Type of appendicitis.	Negative.	White blood cells.	Red blood cells.	Both.
Interval . . . . .	27	2	0	0
Acute suppurative . . . . .	10	1	1	1
With local peritonitis . . . . .	18	7	0	0
With abscess . . . . .	27	6	0	0
With diffuse peritonitis . . . . .	8	3	0	0

The highest proportion of abnormal urinary findings was in the group with local and diffuse peritonitis and with abscess formation, probably the result of the toxic effect on the kidneys or due to an inflammation of the right ureter because of inflammation or infection adjacent to it. Helmholtz<sup>28</sup> reported 8 per cent with urinary symptoms, while Richter<sup>24</sup> found 6 per cent with abnormal urines.

**Leukocyte Count.** The highest counts were found in the cases with abscess formation and with diffuse peritonitis. A leukopenia means a very poor prognosis. The only 2 cases with counts below 5000 died; 1 was 3600 and the other 4950.

The time interval between onset of symptoms and time of operation is a most important factor in forecasting surgical pathology and the ultimate prognosis. In the cases where the disease was localized to the appendix or to the neighboring peritoneum the average time interval was 53 hours; while in the cases with abscess formation and diffuse peritonitis the number of hours was increased to 78.

Nearly every case of acute appendicitis should be operated upon as soon as the diagnosis is made, the exceptions being those cases in which a definite diagnosis of diffuse peritonitis can be made, and also in those where the general condition is so bad that operation would surely prove fatal. In these almost hopeless cases supportive and expectant treatment often allows one to perform appendectomy or drainage later, after the disease has localized itself.

Ethylene and ether usually were the anesthetic agents employed. Complete relaxation of the abdominal walls allows the best exposure, least trauma and least contamination. Right rectus incision was employed 78 times, Battle incision 18 and McBurney 15 times.\* The abdomen was drained in 54 out of 82 acute cases. Ileostomy was done on 1 patient, with a fatal outcome.

The postoperative complications were: Bronchopneumonia, 2; evisceration, 2; fecal fistulae, 1; wound infection (severe), 2; chicken-pox, 1.

The mortality percentage for the entire group of 111 cases was

\* At present the McBurney incision is used in the majority of instances.

6.3. In the interval group it was 0 per cent, while in the acute group, numbering 82 cases, it was 8.4 per cent. The mortality rate for cases over 12 years of age with acute appendicitis of all varieties was 6 per cent. The ages of the 7 patients that died were 4, 5, 9 years and 4 of 11 years. Of the 7 deaths 5 occurred in males.

TABLE 5.—OPERATIVE MORTALITY RATE FOR APPENDECTOMIES IN CHILDREN.

Author.	Year.	Number of cases.	Maximum age.	Mortality, per cent.
Erdmann <sup>14</sup>	1907	100	15	7.0
Riedel <sup>4</sup>	1907	310	10	16.4
Beth <sup>13</sup>	1908	100	12	21.0
Bar <sup>32</sup>	1908	49	10	12.0
Churchman <sup>6</sup>	1909	9	5	22.0
Braman <sup>33</sup>	1909	117	15	17.9
McWilliams <sup>34</sup>	1910	55	10	10.0
		16	5	18.7
Dowd <sup>35</sup>	1910	181	15	6.0
Deaver <sup>16</sup>	1910	500	15	4.6
Mitchell <sup>29</sup>	1912	40	13	25.0
Bellington <sup>2</sup>	1912	115	15	17.8
Fowler <sup>5</sup>	1912	183	12	3.0
Hoffmann <sup>3</sup>	1912	...	10	15.3
Gray <sup>30</sup>	1914	200	12	10.0
Clofton <sup>36</sup>	1915	...	..	4.0
Morf <sup>37</sup>	1917	150	15	8.0
Abt <sup>12</sup>	1917	80	2	50.0
Alexander <sup>17</sup>	1920	500	15	3.0
Helmholz <sup>28</sup>	1924	15	5	47.0
		53	15	5.5
Beekman <sup>18</sup>	1924	145	13	7.5
Bolling <sup>31</sup>	1924	123	15	8.1
Muller <sup>38</sup>	1924	58	15	6.8
Edberg <sup>19</sup>	1926	754	15	5.0
Seeger <sup>20</sup>	1926	61	13	8.2
Farr <sup>21</sup>	1928	889	15	5.9
Peterson <sup>22</sup>	1929	100	6	6.0
Richter <sup>24</sup>	..	208	13	7.2

From the above table one can readily see that the mortality rate is much higher in the lowest age groups.

Postmortem examination was done on 6 out of the 7 patients that died. The cause of death was reported as follows:

1. Embolic pneumonia.
2. Diffuse peritonitis—subdiaphragmatic abscess.
3. Diffuse peritonitis—bronchopneumonia.
4. Diffuse peritonitis.
5. Diffuse peritonitis—ileus, bronchopneumonia.
6. Diffuse peritonitis—ileus.
7. Diffuse peritonitis—ileus.

**Conclusions.** 1. Acute appendicitis is seldom seen before 3 years of age, but then occurs with increasing frequency and especially after 7 years.

2. Appendicitis in children occurs slightly more often in males than in females.

3. The peak seasonal incidence is in the fall.



4. There was a history of recent previous infection elsewhere in the body in 13 per cent of the cases.

5. There was a history of one or more previous attacks in 31 per cent of the cases.

6. There is a fair degree of direct correlation between the clinical picture and the surgical and pathologic findings. Unfortunately, however, the degree of correlation occasionally is poor.

7. A leukopenia in acute appendicitis usually means a fatal outcome.

8. Nineteen per cent of the cases showed abnormal urinary findings.

9. The most frequent cause of death was diffuse peritonitis.

10. The time interval between onset of symptoms and time of operation is probably the most important factor in determining pathology and prognosis; consequently, early diagnosis followed by immediate appendectomy offers the best hope for a low mortality rate.

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# A UNIQUE ANOMALY OF THE BILIARY TRACT. COMMUNICATIONS BETWEEN CYSTIC AND HEPATIC DUCTS WITH OCCLUSION OF COMMON DUCT AND SEPARATE ENTRANCES INTO THE DUODENUM.\*

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IN studying the gall bladder and biliary tract in a series of necropsies on infants a unique anomaly of the bile ducts was found. It seems sufficiently interesting to warrant adding it to those already recorded in the literature. Any such anomaly, of course, is of practical interest to the surgeon.

The anomalies of the bile ducts and gall bladder are varied and numerous in man as well as in certain domestic animals that have been studied, namely: the cat, dog, sheep, calf and pig. Some of these abnormalities have been described by Gessner,<sup>1</sup> Kehr,<sup>2</sup> Schachner,<sup>3</sup> Eisendrath,<sup>4</sup> Morley,<sup>5</sup> Graham,<sup>6</sup> and Boyden.<sup>7</sup> Various types have been described by these writers but none seem to conform exactly to the anomaly found in the case reported below. Flint<sup>8</sup> mentioned the fact that separate entrance of the common hepatic and cystic ducts into the duodenum occurs but gave no authority for this statement.

**Case Report.** L. D., a white female child, aged six weeks, was admitted to the University of Virginia Hospital on July 29, 1930. When she was one week old blood was noticed in the stool, followed two days later by seepage of blood from the umbilical stump, vagina, mouth and eyes. There had been no vomiting and jaundice had not been observed. She was born by a normal delivery at term, had none of the childhood diseases and was breast-fed. Physical examination, on admission, revealed marked jaundice of the skin with excoriations about the anus. The abdomen was distended and tympanitic, and the spleen was palpable below the costal margin. Blood could be seen oozing from the conjunctivæ. Rectal temperature was 99.6°. Laboratory studies showed the urine to be negative; hemoglobin, 50 per cent (Dare); red blood cells, 2,500,000 per c.mm.; white blood cells, 6200 per c.mm. Differential blood smear showed 33 per cent polymorphonuclears, 62 per cent lymphocytes, 2 per cent mononuclears, 2 per cent transitionals and 1 per cent eosinophils. Clotting time and bleeding time were each sixteen minutes, reduced in a week's time to a clotting time of eight minutes and a bleeding time of four minutes. The icterus index five days after admission was 84, and both direct and indirect van den Bergh reactions were positive. Intradermal tuberculin reaction was negative, as was the blood Wassermann. The platelet count was 160,000. A diagnosis of essential purpura hemorrhagica was made.

On the day of admission the patient was given 30 cc. of whole blood

\* Reported through the courtesy of the Department of Pediatrics.

intramuscularly and 23 cc. of citrated blood intravenously. The temperature remained the same and the patient seemed improved, taking feedings regularly. On the third day after admission her temperature went to  $102^{\circ}$  and she lost weight in spite of feedings. A second blood transfusion of 75 cc. of citrated blood was given on the eighth day, but the child died the following day, August 5. There was no vomiting and no bleeding after the first blood was given. The jaundice seemed to deepen.

*Postmortem Report.* A necropsy was done immediately. It revealed marked emaciation, generalized jaundice, an enlarged spleen, atelectasis of the lower lobe of the right lung and a congenital anomaly of the cystic and hepatic ducts.

The entrance of the pancreatic duct into the bowel and the location and derivation of the cystic and hepatic arteries were normal. The common bile duct arose from the duodenum at its normal site (Fig. 1). At

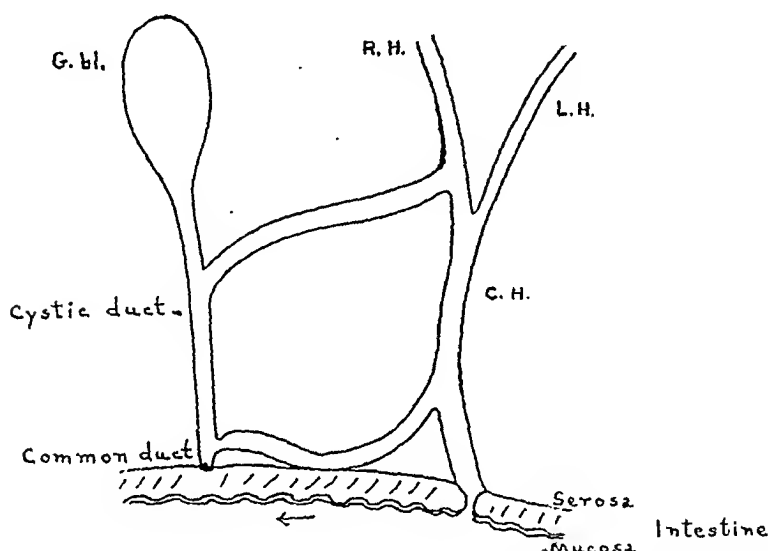


FIG. 1.—Diagrammatic sketch of the anomaly in this case. Arrow indicates the distal direction of the intestine.

a point 3 cm. above this site on the duodenum the common hepatic duct came off. These two vertical ducts were joined by a horizontal duct which came off just above a constriction of the common duct. A second communicating duct was observed high up on the cystic duct, uniting with the right hepatic duct 1 cm. above the bifurcation of the common hepatic. The gall bladder was of normal infant size and color, containing a white mucoid material. Methylene blue injected into the right hepatic duct coursed down the communicating ducts and the common hepatic duct, and entered the duodenum. The gall bladder filled, but no dye entered the duodenum by way of the common duct. Microscopic sections showed acute and chronic pericholangitis.

An explanation of the embryologic mechanism underlying this anomaly may be of great interest. The normal development of the primary evaginations of the liver and pancreas is shown in the diagrammatic sketches of the reconstructions by Stoss (Fig. 2),

and Thyng (Fig. 3). The primary hepatic diverticulum is given off from the duodenum. It branches very early to produce the hepatic duct and the cystic duct, while the proximal end of the original diverticulum elongates to become the common bile duct.

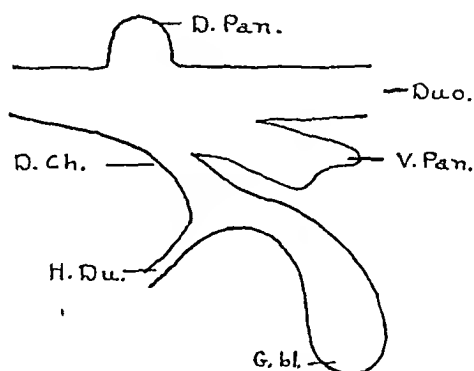


FIG. 2.—Diagram of model of the duodenum and the primary evaginations of the liver and pancreas in a 5-mm. sheep embryo. D. Pan., dorsal pancreas; V. Pan., ventral pancreas; Duo., duodenum; D. Ch., ductus choledochus; G. bl., gall bladder; H. Du., hepatic duct. (After Stoss.)

Soon after, the hepatic duct bifurcates. The gall bladder is formed later by expansion terminally of the cystic duct. Based upon the above reconstructions an attempt may be made to explain the anomaly found in this case.

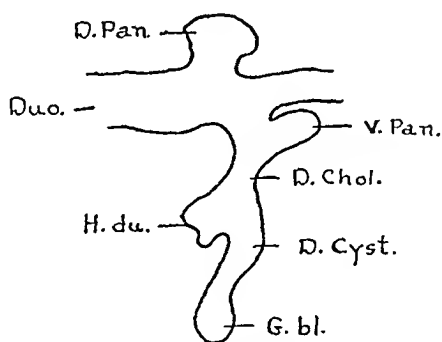


FIG. 3.—Diagram of reconstruction from human embryo, 7.5 mm., of primary evaginations of the liver and pancreas. D. Pan., dorsal pancreas; V. Pan., ventral pancreas; Duo., duodenum; D. Chol., ductus choledochus; G. bl., gall bladder; D. Cyst., ductus cysticus; H. du., hepatic duct. (After Thyng.)

The liver primordium given off from the duodenum failed to elongate normally during the initial stages, according to Jordan.<sup>9</sup> The gut in growing lengthwise appropriated the proximal undivided portion, thus effecting two separate entrances of the biliary ducts into the intestine (Fig. 4). The liver bud then began its normal growth and, due to the close proximity of the cystic and hepatic ducts, connecting branches between the hepatic and cystic ducts were formed from patent remains of earlier hepatic duct evagina-

tions which normally persist as the parietal sacculi of Beale in the wall of the hepatic duct. The gall bladder was formed normally by the dilatation of the distal end of the cystic duct. No definite

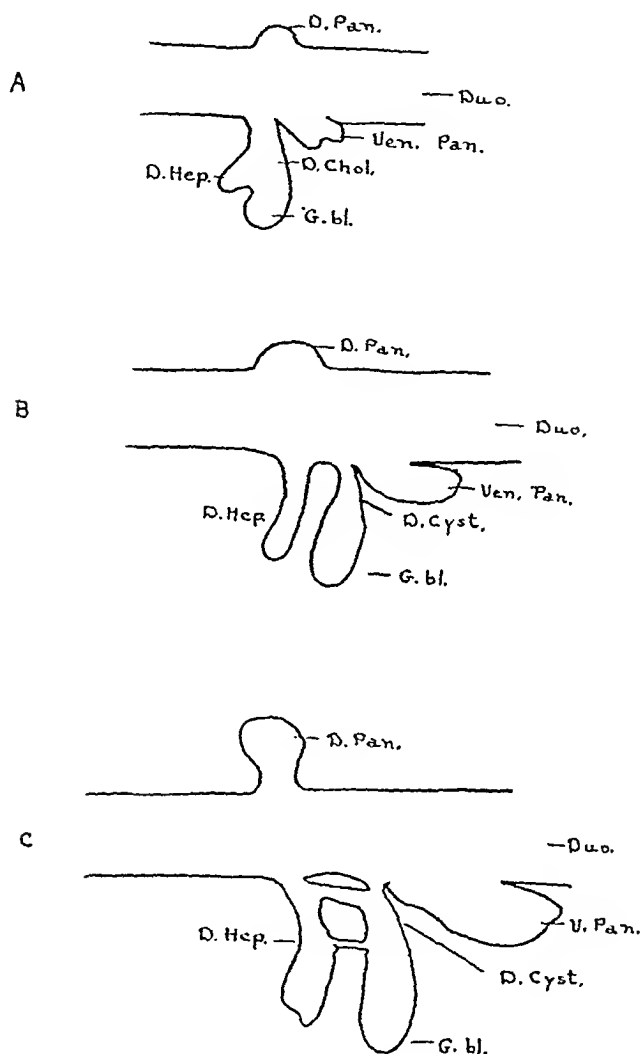


FIG. 4.—Diagrammatic sketch of probable development of the primary evaginations of the liver and pancreas in this case. D. Pan., dorsal pancreas; V. Pan., ventral pancreas; Duo., duodenum; D. Cyst., cystic duct; D. Hep., hepatic duct; G. bl., gall bladder. A, shows failure of liver bud to elongate. B, shows appropriation of proximal portion of bud by the growing gut, effecting separate entrances into the duodenum of the bile ducts; C, shows the connecting branches between the hepatic and cystic ducts being formed.

interpretation is put upon the failure of the common duct to become patent unless its occlusion is purely the result of a mechanical process.

This case presents three interesting features: the common duct and hepatic duct meet the duodenum at separate points, an abnormality of whose existence a surgeon should be cognizant; a communicating duct occurs as high as the cystic and right hepatic ducts; a constriction of the common duct causes its total occlusion. The first two features are of especial interest from an embryologic point of view.

**Summary.** A case is reported in which there are communicating ducts between the hepatic and cystic ducts, separate entrances of the common and hepatic ducts into the duodenum, and an occlusion of the common duct. It is presented as a probably unique congenital anomaly of the biliary tract. An attempt is made to explain the embryologic mechanism underlying this anomaly.

**NOTE.**—Since correcting the printer's proof of this article attention has been called to the article "Anomalous Bile Duets in Man," by S. H. Mentzer, *J. Am. Med. Assn.*, 1929, 93, 1273. The anomaly described above resembles somewhat the normal anatomy in reptiles and some birds as reported by Mentzer.

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#### INTRAHEPATIC LITHIASIS.

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THE case herein reported is unusual in that: (1) The intra-hepatic stones were much larger than any others hitherto encountered, according to the reports in the literature as far back as 1904;

(2) the patient's symptoms were meager considering the tremendous amount of stasis and consequent damage to the liver occasioned by the obstruction; (3) she recovered after operative removal.

**Case Report.** F. G., female, aged forty-five years, housewife, married, was admitted to the hospital on October 8, 1929, with the tentative diagnosis of chronic cholecystitis with cholelithiasis. The chief complaint was itching of the entire body, most marked at night, and pain in the right upper abdominal quadrant referred to the right shoulder. The present illness began about one month ago with itching of the entire body. At that time the itching was accompanied by pain in the upper right abdomen, with loss of appetite and some constipation. About three days before admission the patient was again seized with severe pain in the right upper abdomen. The sharp pain subsided and gave way to a dull ache over the same area. The stools were clay colored, the urine frothy and dark and there was a history of loss of weight of approximately 15 pounds in the last three months. Her past history and family history were entirely irrelevant to the present illness. On physical examination she appeared acutely ill, somewhat emaciated; temperature, 100.2°; pulse, 100; respirations, 26. The scleral conjunctivæ were jaundiced, and there was an icteric tint to the skin over the abdomen, chest and back. There was rigidity and tenderness over the right upper quadrant, most marked over the region of the gall bladder. Scratch marks were numerous. A slight umbilical hernia was noted. Varicosities of both lower extremities were present. With cholecystography the gall bladder failed to fill, but no stone shadows were detected. The Rosenthal-White liver function test revealed complete retention of the dye in the blood stream after thirty minutes.

Upon the diagnosis of cholecystitis and cholelithiasis with obstructive jaundice, she was subjected to operation the following day. The gall bladder was found to be distended and full of calculi. On palpation several stones were found free in the common duct and apparently not producing any obstruction or rather insufficient obstruction to account for the jaundice. The cystic duct was small and contained no calculi. At the point where the left hepatic duct emerged from the lower surface of the liver the end of a calculus was palpated. The hepatic duct at this point was markedly dilated. It was incised and a stone (A), 7 cm. long and 2 cm. in diameter, was removed from the intrahepatic portion of the left hepatic duct. Beyond this still more deeply embedded in the liver was another calculus, 4 cm. long by 2.5 cm. in diameter. Still deeper in the liver structure were many small calculi, varying in size. The right hepatic duct was likewise filled with these small calculi, which were removed through another incision. The incisions in the duct were closed around catheters sewn into both ends and extending deeply into the liver substance. The gall bladder was removed and the stones in the common duct were milked back through the stump of the cystic duct, which was then ligated. A cigarette drain was placed in the foramen of Winslow and the abdomen closed.

The patient had a rather stormy convalescence, necessitating a transfusion on October 14. The drainage from the abdominal wound through the catheters continued; the icterus gradually disappeared, and she was discharged on November 17 in a fairly good condition. When seen three months later the drainage from the abdominal wound had ceased entirely, the wound had healed completely and the patient was gaining weight and appeared in good physical condition. Six months later she developed moderate ascites. There was no edema of the extremities, or other sign of failing circulation. She still has moderate ascites.

Fig. 1, photographed to scale, represents the stones removed in this case. The color of the stones varied from a light yellow to a very dark brown. The large stone (*A*) was very firm in consistency, withstanding considerable rough handling in the operative removal from the intrahepatic portion of the duct. Its lower end was found to fit snugly against a smaller stone which was broken during removal, the fragments of which are represented by *B* and *C*. The smaller stones in the figure were all lying either behind the fragments *B* and *C* in the right hepatic duct or else in the left hepatic duct. All the calculi in this figure were removed from the intrahepatic portion of either the right or left hepatic duct. The gall bladder

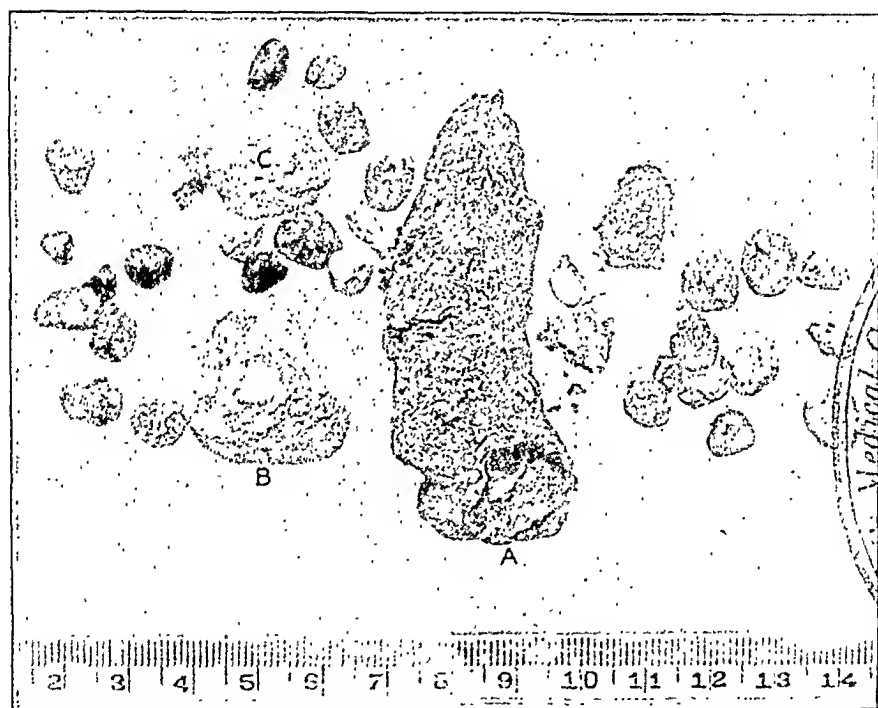


FIG. 1.—Large calculus *A* and smaller calculus represented by fragments *B* and *C*.

calculi and common duct calculi are not included in photograph. Fig. 2 represents a transverse section of the large stone. It is seen to consist of two portions, a cortex and medulla. In the center of the latter there is a fine cleft scarcely visible in the photograph. Cross section of the other small calculi also showed a cortical portion, a medullary portion and a central cleft that Aschoff terms the biliary calculus. Qualitative chemical analysis of the stones showed them all to consist of cholesterol, calcium and bilirubin pigment.

As the result of the accumulation of many individual experiences, the modern conception of the formation of gall stones has been



evolved, and this is set forth in as lucid a manner perhaps as is possible by Aschoff<sup>1</sup> in his "Lectures on Pathology." He classifies all gall stones in three divisions: metabolic stones, those due to infection and those due to stasis. The metabolic type is divided into two classes, one consisting purely of cholesterin and the other consisting of bilirubin. The former are always single, spherical and are found on cross section to consist of radiating crystals of cholesterin. When such a stone becomes impacted in the cystic duct, or when the gall bladder in which it is contained becomes the seat of an infection, the stone changes its character and becomes what is known as a combination stone, consisting of the central cholesterin nucleus, around which is deposited a shell of pigment, calcium and epithelial debris. Another type of metabolic stone is perhaps the pure pigment stone, which occurs in multiple and is ordinarily found in the gall bladder, usually mulberry shaped, rarely



FIG. 2.—Cross-section of large calculus (A) shown in Fig. 1.

oval or circular and never faceted. These stones are the size of a pea, hard, brittle, difficult to handle, very frequently disintegrating into coarse black sand. On cross section they present a metallic sheen, are sometimes brightly colored and are homogeneous without any layer formation and without any distinguishable nucleus or cortex. This stone can also be made into a combination stone by a superimposed infection with layering of cholesterin pigment and calcium.

The infectious type of stone is very characteristic. It occurs in two forms: the faceted calcium pigment cholesterin stone and the cylindrical calcium pigment cholesterin stone. The faceted cholesterin calcium stones are usually tetrahedral in shape. They have a soft, coarse nucleus, usually with more or less broad stellate branching, cleft projections of which reach to the cortex. The cortex is made up of numerous systems of lamellæ, and there is a very gradual transition from nucleus to cortex. The cortex is

harder than the nucleus; the nucleus is usually darker. The stones are usually all similar and very rarely is a second or third generation found from which one may conclude that all stones in a gall bladder have originated at one time and that they grow equally with every new inflammatory attack but that very rarely new stones arise.

The second form of infectious stone, the cylindrical or barrel shaped, has either a faceted surface, where it is in contact with other stones, or a nonfaceted, finely nodular surface, where it is in contact with the mucous membrane.

There is a third manner of gall stone formation in which stasis is the essential factor and which differs from the other two described, in that it takes place only in the bile passages. The resultant stones are composed of bilirubin and calcium. They are more or less soft, fragile, evenly colored, plainly laminated, red brown to brown black, sometimes egg shaped, sometimes round, sometimes sausage shaped or angular. They are most often found around foreign bodies, and the most important of these are gall bladder stones which have wandered away from the gall bladder. Thus we may have a gall bladder stone which has a new shell consisting of soft, earthy, bilirubin calcium rich in cholesterin. The nucleus may be that of any one of the stones previously described.

Infection is the factor which has been most under discussion in the literature. The relation of cholangitis to intrahepatic calculi is quite striking. Beer,<sup>2</sup> in a study of 250 livers of patients who had died of gall stone disease, found intrahepatic lithiasis in 6 cases, in all of which cholangitis was present. (It is interesting to note that these 6 cases also had extrahepatic calculi.) The degree of associated cholangitis varied from a mild catarrhal inflammation to a severe suppurative lesion. Courvoisier<sup>3</sup> found cholangitis in 15 out of 52 cases of stones in the hepatic duct or its branches. In reviewing Kehr's<sup>4</sup> report, Beer found 7 cases of intrahepatic lithiasis accompanied by cholangitis.

The elevation in the pulse rate, particularly in the presence of jaundice, the accelerated respirations and the accompanying rigidity and tenderness in the right upper quadrant are suggestive of some degree of infection of the biliary tract. The vicious cycle of stasis followed by infection and infection producing stasis has been repeatedly demonstrated in biliary disease. That dilatation of the extrahepatic and intrahepatic passages as far back as those of the fifth or seventh order is the invariable accompaniment of cholecystitis is also well known. With the tremendous dilatation and the complete obstruction of the ducts which occurred in our case it is surprising that there were not signs of grave infection of the tract.

**TIME ELEMENT IN STONE FORMATION.** The size of the stones found in our case brings up the question of the time element in their formation. Homens<sup>5</sup> found stones around a suture in the gall bladder in approximately one and a half years. Stones have been

produced experimentally in from three months to one year. The stones so produced were very small. It seems beyond belief that stones such as we described could have been formed in the one month of the patient's illness. Unquestionably these stones existed in the liver for a period of years, during which time she was apparently wholly free from symptoms. This is one of the most striking features of the case. Particularly is this true when one considers the tremendous handicap under which the patient must have been existing, as indicated by the liver function test. It furnished another example of the possibility for the symptomless existence of stones as long as there is no obstruction or severe infection.

**JAUNDICE AND PAIN.** Murchison,<sup>6</sup> in a discussion of intrahepatic calculi, states that they do not cause jaundice, and that they attain considerable size without giving pain. On the other hand, Rolleston<sup>7</sup> believes that all intrahepatic calculi are accompanied by some degree of icterus. That our patient was free from the symptoms of itching and jaundice for so long a period of time during which the stones must have been growing by accretion merely means that there never was a sufficiently complete obstruction to the bile flow. Even at the time of operation the jaundice was not very deep, although the stools were then already clay colored. Apparently the complete blockage was coincident with the onset of severe pain occurring three days before the operation. It probably did not result purely from a mechanical obstruction, but from a low-grade infection causing sufficient edema to completely close the lumen of the hepatic ducts. It is believed logical to conclude that the obstruction causing the icterus occurred here rather than in the common duct in which the small calculi were found to be freely movable.

In all the reported cases pain is the predominating symptom. Whether the pain is due to the intrahepatic or the extrahepatic calculi is a moot question. Again it is significant that, despite the large number and the large size of some of the calculi, pain did not become a factor until within a month of the time of operation.

**HEPATITIS ASSOCIATED WITH INTRAHEPATIC LITHIASIS.** Graham<sup>8</sup> and others have demonstrated the association of hepatitis with chronic cholecystitis. In a recent study of a large series of cases Koster, Goldzieher and Collens<sup>9</sup> confirmed this association, but also suggested, and presented some evidence in favor of the idea contrary to Graham's, that the liver lesion was secondary to and was dependent upon the lesion of the bile passages. While no section was taken from the liver of this patient, it seems hardly likely that it could have escaped a comparatively severe grade of secondary chronic infection. The liver function test showing complete retention of the dye in the blood is indicative of the altered functional state.

The presence of a small liver, found at the operating table, with

the recent development of ascites, not attributable to any other known cause, speaks for a development of cirrhosis of the liver in this patient. Although it is known that there is no direct connection between portal cirrhosis and hepatitis, the liver in this patient has suffered sufficient insult to produce a general intoxication by its altered function, and this may perhaps be said to be the cause of the onset of the ascites.

**TREATMENT.** The treatment is, of course, surgical, consisting of the removal of the stones and drainage of the ducts. While intrahepatic calculi are relatively rare, their recognition at operation will often depend upon the care with which the hepatic ducts are palpated during routine biliary tract surgery.

**Summary.** 1. A case of intrahepatic lithiasis is presented with unusually large-sized stones.

2. A striking feature of this case is the freedom from symptoms during the long period of time in which stone development undoubtedly occurred.

3. A discussion of the causes and associated features of stone development is presented.

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### OBSERVATIONS ON THE CLINICAL APPLICATION OF THE URINE SEDIMENT COUNT (ADDIS).

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THE kidney, in common with other tissues, responds to inflammatory and degenerative processes by the elaboration of a more or less typical cellular reaction. These cellular elements eventually

find their way into the urine. It is reasonable then to conceive that a study of the formed elements in the urine may by their number and character indicate the type of structural change in the kidney from which they are derived. For example, in inflammatory disease mainly affecting the glomeruli, one would expect to find in the urine sediment a quantitative increase over the normal in the number of red blood cells as well as white blood cells. In degenerative lesions, one would expect to find a quantitative increase over the normal of epithelial cells desquamated from the renal tubules.

Haines and Skinner,<sup>1</sup> in 1898, showed that formed elements are present in the urine of normal persons. However, it fell to Addis<sup>2</sup> to establish the fact that the cellular elements of the urine are just as susceptible to quantitative estimation as those of the blood. In another study<sup>3</sup> he further showed that the urine sediment count might be employed to differentiate, on a purely clinical basis, the various types of Bright's disease.

We employed the urine sediment count in studying certain infectious diseases<sup>4,5</sup> and found it to be helpful.

Since congestive heart failure is not infrequently associated with certain forms of Bright's disease, we felt it was necessary to determine the influence of renal passive congestion alone, on the quantitative excretion of formed elements in the urine. No exact data on this question were found available in the literature.\*

Furthermore, the clinical differentiation of active rheumatic carditis and subacute bacterial endocarditis occasionally offers much difficulty. We, therefore, also undertook to determine whether the sediment count, as a single added clinical fact, might be useful in this differentiation.

The technique for performing the urine sediment count was exactly as originally described by Addis.<sup>3</sup> On the day previous to the test the patient is asked to restrict fluid intake in order to submit a specimen of sufficient concentration to preserve hyalin casts.<sup>3</sup> Before retiring the bladder is completely emptied. Since the count is based on the 12-hour excretion, the specimen is best collected 12 hours after the last voiding. Where this is not possible a 6- or 9-hour specimen may be collected and a correction made in the calculation on the basis of a 12-hour excretion. Males void directly into the specimen bottle to prevent loss of any urine. Females must be catheterized to avoid contamination.† After carefully measuring the total volume voided it is thoroughly shaken

\* Since this manuscript was prepared, the following study appeared: The Number of Formed Elements in the Urinary Sediment of Patients Suffering from Heart Disease, with Particular Reference to the State of Heart Failure. Stewart, H. J., and Moore, N. S.: *J. Clin. Invest.*, December 20, 1930, 9, 409.

† The collection of specimens for this quantitative procedure must be carried out with exactitude. The special nursing staff required was paid for in part from the funds of the Committee for Encouragement of Medical Research (Rheumatic Fever) and in part from the Crane Fund.

and 10 cc. placed in an Addis centrifuge tube.\* This is centrifuged for fifteen minutes at about 1800 revolutions. After centrifuging, 9 cc. of supernatant urine is drawn off for the protein determination and the sediment is thoroughly mixed in the remaining 1 cc. When the sediment is heavy it may be mixed in 2 to 5 cc. of urine; when it is small in amount it is mixed in 0.5 cc. of urine and allowance made in the final calculation.

One drop of this sediment mixture is placed on a blood-counting chamber. Casts are counted with the low-power objective over the entire ruled area, representing a volume of 0.0009 cc. Red blood cells and white and epithelial cells are counted with the high-power objective over one small ruled area, representing a volume of 0.0001 cc. An average is taken of four to six different fields in the cast count and six to ten fields in the count of the other formed elements. A differential cast count is made at the same time as the total count.

From the average figures obtained in this way the calculation of the total 12-hour excretion rate of the formed elements is fairly simple. Addis has constructed a formula for this calculation.†

There are certain elements in the technique of this procedure which one acquires only after experience with the method. Casts must be distinguished from cylindroids. Red blood cells considered significant of glomerular origin are often faint, hemoglobinless rings or "ghosts," whereas red cells originating from somewhere in the genitourinary tract below the glomerulus are often sharply defined, biconcave and hemoglobin-filled. Since white blood cells are often indistinguishable from small round epithelial cells of the same approximate size derived from the tubules, they are counted together. However, Addis<sup>3</sup> noted that in glomerular inflammatory lesions white blood cells predominated over the epithelial cells in numbers, while in tubular degenerative lesions the reverse was true. Flat epithelium from the surface lining of the bladder and large round epithelium from the deeper layers of the genitourinary tract are not included in the count. The large variation in the count of these cells in normal persons may be accounted for by the inclusion of a number of these cells from the prostate and other glands of the genitourinary tract. However, Addis<sup>3</sup> showed that the count of these cells in the presence of an active renal lesion so far exceeds the usual count in persons without renal disease, as to make the standard set entirely satisfactory. It should be understood that this procedure is by no means meant to be strictly exact quantitatively

\* These tubes may be obtained through Arthur H. Thomas Company, Philadelphia, U. S. A.

† Number counted  $\times \frac{\text{vol. in cc. in which sediment was mixed}}{\text{vol. in cc. in which count was made}} \times \frac{\text{vol. in cc. per 12 hours}}{10}$

TABLE 1.—URINE SEDIMENT COUNT IN NORMAL PERSONS.

Number.	pH.	Sp. Gr.	Urine volume, cc. per 12 hrs.	Protein,* mg. per 12 hrs.	Red cells, millions per 12 hrs.	White and epithelial cells, millions per 12 hrs.	Cast,† thousands per 12 hrs.
1 . . . . .	5.0	1.030	369	5.3	0.0	0.22	9.2
2 . . . . .	5.0	1.040	259	18.0	0.0	0.064	0.0
3 . . . . .	5.0	1.031	473	10.2	0.0	0.118	0.0
4 . . . . .	5.5	1.023	355	12.78	0.0	0.117	0.0
5 . . . . .	5.0	1.044	208	8.9	0.0	0.062	0.0
6 . . . . .	5.0	1.020	616	22.1	0.0	0.077	0.0
7 . . . . .	5.5	1.010	776	8.38	0.0	0.580	0.0
8 . . . . .	5.0	1.027	228	32.8	0.0	0.3	3.8
9 . . . . .	5.8	1.027	408	57.7	0.0	0.73	0.0
10 . . . . .	5.5	1.027	269	23.12	0.0	0.67	2.2
11 . . . . .	6.7	1.032	186	26.8	0.0	0.6	4.1
12 . . . . .	5.6	1.028	337	24.8	0.0	0.4	0.0
13 . . . . .	5.0	1.036	147	.....	0.009	0.082	0.0
14 . . . . .	5.8	1.030	259	18.6	0.010	0.79	0.0
	5.7	1.028	234	16.8	0.26	1.1	7.8
15 . . . . .	5.5	1.028	285	42.0	0.01	0.81	3.2
16 . . . . .	5.0	1.040	158	5.6	0.013	0.115	0.0
17 . . . . .	5.5	1.018	145	10.4	0.02	0.29	2.2
18 . . . . .	5.0	1.035	170	18.3	0.02	0.36	0.0
19 . . . . .	5.0	1.028	80	5.75	0.022	0.52	0.0
20 . . . . .	5.5	1.032	335	21.7	0.027	1.36	
21 . . . . .	5.5	1.026	343	17.2	0.028	0.056	0.0
22 . . . . .	5.0	1.038	274	60.2	0.034	0.18	0.0
23 . . . . .	6.5	1.027	360	25.9	0.04	0.47	2.0
24 . . . . .	5.5	1.022	344	49.5	0.05	0.27	1.8
	5.0	1.027	186	26.6	0.09	0.72	1.03
25 . . . . .	5.5	1.036	226	26.18	0.06	0.19	0.0
26 . . . . .	5.8	1.029	239	29.3	0.07	0.37	0.0
27 . . . . .	5.7	1.020	363	52.2	0.07	0.7	2.0
28 . . . . .	5.0	1.032	287	15.4	0.071	0.262	0.0
29 . . . . .	6.5	1.024	387	13.9	0.072	0.097	0.0
30 . . . . .	5.0	1.034	137	2.9	0.076	0.34	0.0
31 . . . . .	5.3	1.034	220	.....	0.088	0.638	0.0
32 . . . . .	5.0	1.034	120	7.76	0.127	3.4	0.5
33 . . . . .	5.5	1.037	187	26.9	0.13	0.28	2.1
34 . . . . .	5.5	1.030	237	34.2	0.14	0.63	2.6
35 . . . . .	5.0	1.036	414	17.88	0.145	0.028	0.0
36 . . . . .	5.5	1.042	210	9.0	0.157	0.131	0.0
37 . . . . .	6.5	1.026	385	22.1	0.159	0.192	0.0
38 . . . . .	5.5	1.027	205	10.2	0.205	.....	0.0
39 . . . . .	6.0	1.031	312	33.7	0.16	0.81	0.0
	5.0	1.030	348	30.1	0.20	0.87	3.8
40 . . . . .	5.8	1.031	256	28.7	0.21	0.32	0.0
41 . . . . .	5.5	1.033	384	46.0	0.3	0.83	6.4
42 . . . . .	5.5	1.028	302	6.48	0.39	1.04	0.0
43 . . . . .	5.0	1.030	293	42.2	0.56	2.43	0.0
44 . . . . .	5.0	1.033	218	22.3	0.65	1.27	4.8
45 . . . . .	5.5	1.038	355	15.33	0.931	0.047	3.9
	5.0	1.043	280	10.0	1.53	0.024	0.0
Average . . . . .	...	.....	...	21.8	0.146	0.540	1.29

\* Centrifuge method (see reference 6).

† All were of hyalin variety.

and for clinical purposes need not be so, because in interpreting the sediment count one is concerned with numbers which often range in the hundreds of thousands, millions and in some instances billions. Likewise, sufficient leeway is allowed between the upper limit of normal counts and the lower limit of those considered abnormal.

Protein excretion was determined by the method described by Shevsky and Stafford.<sup>6</sup>

Table 1 shows the results of forty-nine counts in 45 medical students in whom there was no reason to suspect past or present renal disease. It shows the average and range of variation in the 12-hour excretion rate of the formed elements. We have accepted as the upper limit of normal excretion in 12 hours: red blood cells, 500,000; white blood cells and epithelial cells, 1,000,000; casts, 5000. With very few exceptions, these figures are well above the upper range and considerably above the observed averages. The "normal" limits we have set were exceeded only four times in the "normal" cases, by the red blood cells, twice by the white blood cells and three times by the casts. While one may wish to apportion our normal upper limits somewhat differently, it is well to remember that exact figures are almost impossible of attainment. Also, that the entire procedure must be accepted as only a single added clinical fact and its usefulness is dependent upon its correlation with other available clinical data.

Table 2 serves to indicate that the diagnosis of microscopic hematuria may be impossible unless the urine volume is taken into consideration as well as the concentration of the formed elements to be counted.

TABLE 2.—THE VALUE OF THE URINE SEDIMENT COUNT IN THE DIAGNOSIS OF MICROSCOPIC HEMATURIA.

Urine volume, cc. per 12 hrs.	No. of R. B. C. in 10 H. P. F. (concentration).	Twelve-hour output of R. B. C. in urine (excretion rate).	Interpretation.
100 . . . . .	1.0	160,000	Normal
200 . . . . .	1.0	320,000	Normal
1,000 . . . . .	1.0	1,600,000	Hematuria
2,000 . . . . .	1.0	3,200,000	Hematuria

In Table 3 are listed nineteen quantitative counts of the formed elements in the urine sediment of 10 patients with acute, subacute and chronic glomerulonephritis. Since it was of great importance for our present purpose to be certain of the diagnosis in these patients, due precautions were taken to choose a selected group. The diagnosis of glomerulonephritis in Patients 3 and 5 was confirmed by necropsy. Patient 1 developed edema, hypertension and renal insufficiency under our observation, while convalescing from lobar pneumonia. The rest of this group consisted of patients with azotemia or marked renal insufficiency and anemia, as well as the history and usual clinical course of glomerulonephritis.



TABLE 3.—STUDY OF THE TWELVE-HOUR EXCRETION RATE OF FORMED ELEMENTS IN THE URINE OF PATIENTS WITH DIFFUSE GLOMERULONEPHRITIS.

Name. No.	Date.	Urine volume, cc. per 12 hrs.		Specific gravity.	Protein, mg. per 12 hrs.	R. B. C. in millions per 12 hrs.	White and epithelial cells in millions per 12 hrs.	Casts per twelve hours in thousands.				
		pH.						Total.	Hyalin.	Granular.	W. B. C. and epithelial.	Blood.
A . . . 1	4/ 9/30	143	5.0	1.010	2162	13.41	5.18	1120	1000	120	0	0
	4/12/30	251	5.0	1.013	2349	37.37	7.91	2649	149	2500	0	0
	5/15/30	1520	5.0	1.007	4370	1157.0	0.15	0	0	0	0	0
	6/11/30	473	5.5	1.007	683	299.0	45.44	972	72	900	0	0
	7/30/30	...	...	1.011	...	115.6	8.82	350				
D . . . 2	3/ 9/30	746	5.0	1.010	7520	490.49	33.57	11605	11605	0	0	0
	1/20/30	980	5.0	1.016	8050	20.58	36.06	971	485	480	6	0
	12/11/29	578	5.5	1.015	12484	38.0	0.94	0	0	0	0	0
	10/ 1/29	798	5.0	1.020	5460	44.7	15.96	5320	320	5000	0	0
	10/16/29	826	5.0	1.024	8326	32.2	8.67	12711	711	12000	0	0
B . . . 6	6/24/30	325	5.5	1.010	76	3.76	2.6	966	800	123	43	0
	9/ 9/30	514	5.0	1.011	384	8.89	10.95	14	14	0	0	0
	9/26/30	492	6.8	1.010	45	41.20	3.30	150	125	0.3	25	0
	9/ 9/30	585	7.4	1.012	273	4.97	107.4	194	194	0	0	0
	9/15/30	677	7.5	1.010	146	13.80	47.7	0	0	0	0	0
M . . . 9	9/30/30	195	6.8	1.014	31	46.41	1.2	173	173	0	0	0
	10/ 4/30	295	5.0	1.018	148	43.0	2.9	82	82	0.5	0	0
	10/23/30	576	5.0	1.012	321	27.8	2.0	55	55	0.5	0	0
	10/28/30	822	7.5	1.004	....	2.88	4.1	22	22	0	0	0

TABLE 4.—STUDY OF THE TWELVE-HOUR EXCRETION RATE OF FORMED ELEMENTS IN THE URINE OF PATIENTS WITH CONGESTIVE HEART FAILURE.

Name.	No.	Date.	Urine volume, cc. per 12 hrs.		Specific gravity.	Protein, mg. per 12 hrs.	R. B. C. in millions per 12 hrs.	White and epithelial cells in millions per 12 hrs.	Casts per twelve hours, in thousands.				
			pH.						Total.	Hyalin.	Granular.	W. B. C. and epithelial.	Blood.
Ba . . . 1	2/24/30	373	5.0	1.012	393	0.31	18.64	213	172	27.5	13.5	0	0
	4/29/30	198	5.5	1.015	206	0.2	9.56	687	655	32.5	0	0	0
	11/16/29	955	7.0	1.020	343	0.0	0.95	0	0	0	0	0	0
	7/20/29	222	5.0	1.030	411	0.04	0.64	144	83	61.7	0	0	0
	2/ 1/30	194	5.0	1.028	2880	0.25	2.18	3915	3740	108	67.5	0	0
Ca . . . 2	10/ 9/29	524	5.5	1.016	113	0.0	0.26	0	0	0	0	0	0
	10/17/29	189	5.0	1.032	231	0.0	1.56	183	157	26.3	0	0	0
	11/ 5/29	1712	5.5	1.006	61	0.21	41.94	166	166	0	0	0	0
	11/26/29	400	5.0	1.034	2016	0.42	0.42	19	19	0	0	0	0
	12/ 3/29	470	5.0	1.030	186	0.18	1.29	19	19	0	0	0	0
Cb . . . 3	11/ 1/29	238	5.0	1.014	15	0.11	0.06	0	0	0	0	0	0
	10/ 3/29	252	5.0	1.032	36	0.0	0.15	336	245	91	0	0	0
	10/ 9/29	192	5.0	1.030	45	0.0	0.1	48	29	18.6	0	0	0
	10/21/29	46	5.0	1.030	49	0.01	0.18	23	21	2	0	0	0
	2/25/30	123	5.0	1.022	39	0.03	3.07	43	26	17	0	0	0
Da . . . 4	1/18/30	131	5.0	1.034	330	0.02	1.83	0	0	0	0	0	0
	2/ 5/30	273	5.5	1.025	481	0.07	3.03	47539	47500	0	59	0	0
	12/ 4/29	332	5.0	1.026	143	0.21	0.58	0	0	0	0	0	0
	10/15/29	735	5.5	1.022	105	0.0	4.23	81	40	40.8	0	0	0
	2/26/30	347	5.0	1.015	2998	0.65	1.21	192	192	0	0	0	0
Fa . . . 5	9/11/29	206	5.0	1.028	29	0.10	1.66	0	0	0	0	0	0
	10/ 1/29	461	5.0	1.022	128	0.0	1.28	0	0	0	0	0	0
	11/12/29	296	5.0	1.028	42	0.01	0.81	16	16	0	0	0	0
	3/ 9/30	348	5.0	1.010	225	2.61	0.52	104	31	0	70	0	0
	10/ 1/29	1062	6.5	1.012	229	0.93	45.14	13	13	0	0	0	0
Fb . . . 6	5/16/30	609	5.0	1.011	153	0.0	1.98	0	0	0	0	0	0
	4/28/30	396	5.0	1.021	2708	0.97	6.24	2342	1753	587.5	0	0	0
	4/28/30	507	5.5	1.020	1825	0.25	1.9	9601	9100	504.8	0	0	0
	1/15/30	427	5.5	1.030	123	0.12	1.71	0	0	0	0	0	0
	1/28/30	395	5.0	1.024	85	0.53	0.33	0	0	0	0	0	0
Ga . . . 7	2/ 4/30	288	5.0	1.025	58	0.32	0.23	0	0	0	0	0	0
	9/11/30	450	5.8	1.020	81	0.07	1.12	140	140	0	0	0	0
	9/17/30	200	5.5	1.024	43	0.15	2.44	0	0	0	0	0	0
	10/ 8/30	164	5.5	1.020	153	0.66	1.77	152	152	0	0	0	0
	10/ 4/30	440	5.0	1.020	216	0.44	27.72	122	122	0	0	0	0
Hb . . . 8	10/ 8/30	288	5.0	1.030	88	0.86	43.20	1942	1400	542	0	0	0
	10/ 9/30	246	5.0	1.016	283	0.57	8.36	410	410	0	0	0	0
	10/28/30	240	6.8	1.015	...	0.56	123.8	0	0	0	0	0	0

In Table 4 the same observation is repeated thirty-eight times in 26 patients with congestive heart failure. While the excretion rate of protein, white and epithelial cells and casts is comparable in both conditions, there is a striking difference in the excretion rate of red blood cells. In active glomerulonephritis microscopic hema-

TABLE 5.—QUANTITATIVE STUDY OF THE TWELVE-HOUR URINE SEDIMENT COUNT IN ACUTE RHEUMATIC INFECTION.

Name.	No.	Date.	Urine volume, cc. per 12 hrs.	pH.	Specific gravity.	Protein, mg. per 12 hrs.	R. B. C. in millions per 12 hrs.	White and epithelial cells in millions per 12 hrs.	Casts per twelve hours, in thousands.					
									Total.	Hyalin.	Granular.	Epithelial.	Blood.	Temperature, °F.
Aa	1	4/ 8/30	310	5.0	1.021	89	0.00	3.23	0	0	0.0	0.0	0.0	99.4
Ba	2	5/ 2/29	513	5.0	1.024	2954	3.00	28.00	6000	6000	0.0	0.0	0.0	103.4
		5/14/29	358	5.5	1.032	25	5.75	32.76	14	14	0.0	0.0	0.0	99.6
		5/15/29	255	5.5	1.034	18	4.03	6.82	21	21	0.0	0.0	0.0	100.2
		5/29/29	605	6.0	1.024	13	0.69	3.73	36	36	0.0	0.0	0.0	99.8
		6/ 4/29	1174	6.5	1.024	50	0.73	3.52	0	0	0.0	0.0	0.0	98.4
		7/31/29	303	5.0	1.030	15	0.35	1.59	2	2	0.0	0.0	0.0	98.6
		11/22/29	308	5.5	1.020	60	0.25	0.10	0	0	0.0	0.0	0.0	98.6
Bb	3	4/16/29	464	6.5	1.030	33	0.75	0.46	0	0	0.0	0.0	0.0	101.0
Ca	4	1/25/30	70	5.0	1.018	22	0.003	1.82	0	0	0.0	0.0	0.0	102.6
Cd	5	5/11/29	300	5.5	1.030	32	1.20	5.00	217	176	41.0	0.0	0.0	103.4
		5/15/29	255	5.0	1.030	16	0.77	2.87	0	0	0.0	0.0	0.0	103.4
		5/21/29	552	5.5	1.034	50	14.64	531.46	0	0	0.0	0.0	0.0	102.4
		6/ 5/29	458	5.5	1.016	92	3.21	292.97	0	0	0.0	0.0	0.0	103.2
		6/14/29	238	5.0	1.022	15	0.06	22.68	6	6	0.0	0.0	0.0	100.0
		7/18/29	88	5.0	1.026	38	0.03	0.38	2	2	0.0	0.0	0.0	99.0
Da	6	2/ 6/30	600	5.5	1.024	2100	36.00	5.10	16	0	0.0	0.0	16.6	102.2
		2/17/30	828	5.0	1.012	59	2.38	1.55	23	23	0.0	0.0	0.0	101.8
		2/22/30	580	5.0	1.012	41	2.32	1.16	8	8	0.0	0.0	0.0	102.2
		3/ 6/30	607	5.0	1.012	43	1.12	1.67	0	0	0.0	0.0	0.0	99.6
Db	7	4/30/29	404	5.5	1.022	37	0.50	3.00	0	0	0.0	0.0	0.0	104.2
		5/ 8/29	348	5.5	1.027	50	0.70	1.00	60	34	26.0	0.0	0.0	100.0
		5/22/29	312	5.0	1.016	28	0.61	0.39	33	33	0.0	0.0	0.0	99.4
		6/ 3/29	210	5.0	1.036	15	0.00	0.37	49	35	14.3	0.0	0.0	99.6
		6/11/29	374	5.0	1.032	26	0.23	0.65	62	62	0.0	0.0	0.0	99.6
		6/17/29	320	5.5	1.036	18	0.16	0.44	53	53	0.0	0.0	0.0	99.2
		6/26/29	270	5.5	1.036	15	0.03	0.27	22	22	0.0	0.0	0.0	98.8
Dc	8	3/12/29	220	5.0	1.030	trace	0.60	1.00	24	21	0.0	3.0	0.0	101.8
		3/28/29	387	5.0	1.030	54	0.30	0.90	0	0	0.0	0.0	0.0	99.8
		4/ 8/29	398	5.0	1.030	14	0.30	0.15	0	0	0.0	0.0	0.0	100.0
		4/13/29	265	5.0	1.025	48	0.40	0.50	0	0	0.0	0.0	0.0	99.4
		4/20/29	303	5.0	1.030	21	0.50	0.30	0	0	0.0	0.0	0.0	99.6
Dd	9	11/29/29	236	5.5	1.036	17	0.00	0.24	0	0	0.0	0.0	0.0	101.8
		12/ 3/29	244	5.5	1.032	17	0.06	0.20	0	0	0.0	0.0	0.0	99.0
		12/30/29	186	5.0	1.020	13	0.00	0.02	0	0	0.0	0.0	0.0	98.6
		2/11/30	225	5.0	1.020	0	0.52	0.03	0	0	0.0	0.0	0.0	99.0
		4/ 7/30	267	5.5	1.017	15	0.09	0.00	0	0	0.0	0.0	0.0	99.0
De	10	4/24/29	582	5.0	1.026	111	5.00	1.00	366	86	45.0	65.0	0.0	101.0
		5/ 6/29	590	5.0	1.024	42	0.74	7.00	196	17	162.0	17.0	0.0	99.6
		5/14/29	640	5.5	1.024	32	0.16	2.62	160	160	0.0	0.0	0.0	98.6
		5/23/29	760	5.0	1.020	19	0.38	1.42	63	63	0.0	0.0	0.0	99.2
		6/ 3/29	540	5.0	1.028	18	0.24	2.12	60	60	0.0	0.0	0.0	99.2
		6/11/29	385	5.5	1.014	12	0.00	0.11	6	6	0.0	0.0	0.0	98.0
		8/ 8/29	500	5.5	1.026	25	0.13	0.56	0	0	0.0	0.0	0.0	98.0
Fa	11	3/13/29	270	5.5	1.032	15	0.09	0.19	12	4	4.0	4.0	0.0	99.0
		3/21/29	385	5.5	1.030	13	0.14	0.50	10	10	0.0	0.0	0.0	99.0
Ha	12	3/18/29	447	5.5	1.040	0	1.40	1.00	51	0	34.0	23.0	0.0	101.0
		3/27/29	107	5.0	1.040	50	0.20	2.00	2	0	0.0	0.0	0.0	100.0
		4/ 5/29	413	5.0	1.028	29	2.00	12.00	15	0	7.7	7.7	0.0	100.8
		4/12/29	325	5.0	1.040	35	4.00	11.00	0	0	0.0	0.0	0.0	100.0
		4/19/29	790	5.0	1.024	39	0.50	4.00	0	0	0.0	0.0	0.0	99.8
		5/17/29	470	5.5	1.020	50	3.70	6.29	6	6	0.0	0.0	0.0	99.6
		5/24/29	410	5.0	1.030	29	1.72	0.41	11	0	11.4	0.0	0.0	98.2
		6/1 /29	600	5.0	1.028	32	0.12	0.64	100	100	0.0	0.0	0.0	98.1
		6/13/29	783	5.0	1.020	16	0.39	0.29	87	87	0.0	0.0	0.0	99.2
		6/17/29	548	5.5	1.022	17	0.34	0.48	38	38	0.0	0.0	0.0	99.2
		6/26/29	230	5.0	1.042	13	0.64	1.34	97	97	0.0	0.0	0.0	99.2

TABLE 5.—QUANTITATIVE STUDY OF THE TWELVE-HOUR URINE SEDIMENT COUNT IN ACUTE RHEUMATIC INFECTION—(Continued).

Name.	No.	Date.	Urine volume, cc. per 12 hrs.	pH.	Specific gravity.	Protein, mgm. per per 12 hrs.	R. R. C. in millions 12 hrs.	White and epithelial cells in millions per 12 hrs.	Casts per twelve hours, in thousands.					
									Total.	Ilyalin.	Granular.	Epithelial.	Blood.	Tempera- ture, °F.
Ka	13	11/13/29	788	5.0	1.026	532	1.75	1.36	86	21	65.2	0.0	0.0	103.0
		11/27/29	240	5.5	1.036	17	0.36	0.27	0	0	0.0	0.0	0.0	102.2
		12/ 3/29	330	5.0	1.034	83	0.21	0.83	18	9	9.1	0.0	0.0	100.2
		12/28/29	658	5.5	1.016	47	0.08	0.74	36	27	0.0	9.1	0.0	99.0
		2/18/30	506	5.0	1.022	124	0.75	0.51	0	0	0.0	0.0	0.0	99.2
La	14	3/ 5/30	247	5.0	1.026	53	1.58	0.07	3	3	0.0	0.0	0.0	98.6
		3/13/29	364	5.5	1.032	trace	9.00	2.00	7	0	0.0	7.0	0.0	100.4
		3/16/29	804	5.0	1.025	trace	2.60	2.80	78	22	55.6	0.0	0.0	101.0
		3/27/29	253	5.0	1.032	36	0.60	0.50	0	0	0.0	0.0	0.0	98.8
		4/ 5/29	368	5.5	1.030	13	0.40	1.50	0	0	0.0	0.0	0.0	99.0
Lb	15	4/29/29	423	5.0	1.030	176	2.80	7.00	47	31	0.0	15.5	0.0	99.0
		5/ 6/29	350	5.0	1.026	35	0.18	1.00	0	0	0.0	0.0	0.0	99.0
		5/29/29	262	5.5	1.034	5	0.06	0.02	0	0	0.0	0.0	0.0	99.6
		3/20/29	153	6.0	1.028	10	0.60	0.80	0	0	0.0	0.0	0.0	102.4
		4/ 1/29	318	6.0	1.030	20	0.40	2.00	0	0	0.0	0.0	0.0	101.0
Ma	16	4/ 9/29	594	5.5	1.030	64	2.50	42.00	0	0	0.0	0.0	0.0	99.8
		4/17/29	535	5.0	1.032	26	0.50	8.00	0	0	0.0	0.0	0.0	98.6
		5/21/29	410	5.5	1.022	44	0.20	2.87	0	0	0.0	0.0	0.0	98.4
		5/14/29	216	5.0	1.018	1162	0.05	2.20	1080	108	972.0	0.0	0.0	104.0
		6/10/29	152	5.0	1.038	455	1.42	4.19	52	52	0.0	0.0	0.0	99.4
Mb	17	7/17/29	380	5.0	1.026	8	0.53	3.69	100	100	0.0	0.0	0.0	99.4
		3/16/29	388	5.0	1.034	0	0.78	0.97	0	0	0.0	0.0	0.0	100.8
		4/ 3/29	435	5.5	1.030	93	4.50	0.30	0	0	0.0	0.0	0.0	100.0
		4/ 8/29	580	5.5	1.020	8	17.00	0.60	0	0	0.0	0.0	0.0	99.4
		4/13/29	530	5.5	1.030	38	10.40	0.46	0	0	0.0	0.0	0.0	98.6
Mc	18	3/19/29	376	5.0	1.030	0	10.40	0.60	22	8	8.8	4.4	0.0	102.0
		3/28/29	400	5.0	1.024	57	0.50	0.50	44	26	13.2	4.4	0.0	99.8
		4/ 9/29	373	5.5	1.020	26	0.80	0.25	93	70	20.0	3.0	0.0	100.0
		4/17/29	817	5.8	1.020	58	0.50	0.70	22	22	0.0	0.0	0.0	100.6
		4/23/29	258	5.0	1.032	2600	1.60	1.00	86	0	86.0	0.0	0.0	104.6
Na	19	5/ 7/29	261	5.0	1.030	60	1.60	2.00	29	0	29.0	0.0	0.0	100.0
		5/16/29	390	6.5	1.020	20	0.30	0.40	103	27	76.0	0.0	0.0	99.5
		5/24/29	698	5.0	1.024	49	1.14	1.15	209	209	0.0	0.0	0.0	99.0
		6/ 1/29	760	6.5	1.023	38	0.43	0.43	84	84	0.0	0.0	0.0	99.2
		6/ 7/29	587	6.0	1.022	42	0.63	0.83	0	0	0.0	0.0	0.0	99.0
Oa	20	6/13/29	570	5.5	1.024	16	0.93	0.42	31	23	7.9	0.0	0.0	99.0
		7/18/29	705	5.0	1.020	26	0.06	0.39	11	11	0.0	0.0	0.0	99.0
		2/19/30	348	5.0	1.022	37	0.25	2.75	1	1	0.3	0.0	0.0	99.6
		3/18/29	1350	5.5	1.012	mod.	5.00	13.00	30	0	22.5	7.5	0.0	103.6
		3/26/29	604	5.0	1.020	34	3.00	8.00	39	19	15.8	4.2	0.0	102.0
Pa	21	4/ 2/29	536	6.0	1.026	57	0.26	0.34	0	0	0.0	0.0	0.0	102.0
		4/25/29	367	5.0	1.030	36	0.50	3.50	56	14	42.0	0.0	0.0	99.4
		5/11/29	213	5.0	1.030	15	0.20	0.90	15	9	3.0	3.0	0.0	98.6
		2/20/30	564	5.0	1.022	60	1.83	8.87	0	0	0.0	0.0	0.0	101.4
		3/ 7/30	716	5.5	1.016	103	0.72	1.43	79	59	19.9	0.0	0.0	99.6
Ra	23	2/27/30	337	5.0	1.024	15	2.02	28.79	0	0	0.0	0.0	0.0	103.4
Rb	24	2/10/30	58	5.0	1.026	83	0.80	0.17	0	0	0.0	0.0	0.0	104.2
Re	25	2/26/30	644	5.5	1.015	69	0.24	2.66	0	0	0.0	0.0	0.0	99.2
		3/ 6/30	349	5.0	1.015	25	1.45	1.53	0	0	0.0	0.0	0.0	99.4
		3/13/30	460	5.0	1.011	49	0.92	1.73	0	0	0.0	0.0	0.0	99.6
		2/10/30	494	6.0	1.016	105	0.06	0.37	6	6	0.0	0.0	0.0	103.0
		3/ 5/30	135	5.0	1.021	19	0.07	1.22	15	15	0.0	0.0	0.0	101.8
Sa	26	4/25/30	745	5.0	1.018	107	0.25	53.83	20	20	0.0	0.0	0.0	104.0
Sb	27	5/22/30	2100	5.0	1.007	77	0.00	2.36	192	192	0.0	0.0	0.0	100.6
Sb	27	2/ 5/30	562	5.0	1.016	121	2.39	7.03	65	54	0.0	13.6	0.0	99.8
Sc	28	3/11/29	1245	5.0	1.012	0	0.20	0.45	76	55	14.0	7.0	0.0	99.6
Ta	29	4/16/29	303	6.5	1.040	872	5.50	1.35	0	0	0.0	0.0	0.0	105.6
Un	30	4/20/29	654	5.5	1.030	882	11.00	3.00	0	0	0.0	0.0	0.0	103.0
		5/ 1/29	413	5.5	1.030	29	1.50	8.00	23	11	11.5	0.0	0.0	99.6
		3/21/29	315	5.0	1.035	31	0.50	1.0	35	8	26.3	0.0	0.0	101.6
		4/ 2/29	587	6.0	1.022	63	0.60	1.00	0	0	0.0	0.0	0.0	101.0
		4/11/29	385	5.5	1.030	8	0.30	7.00	59	21	26.8	10.8	0.0	102.0
Wa	31	4/18/29	425	5.0	1.030	30	0.30	4.50	12	6	6.0	0.0	0.0	102.0
		3/19/29	445	5.0	1.024	0	0.10	1.00	74	37	21.7	12.3	0.0	103.6
		4/ 4/29	323	5.0	1.036	34	2.20	2.50	0	0	0.0	0.0	0.0	99.6
		4/11/29	400	5.0	1.030	13	0.30	0.55	44	11	33.0	0.0	0.0	99.0

turia was present in each examination. It was persistent where counts were repeated and often of marked degree. However, in the renal passive congestion microscopic hematuria (upper limit of normal red blood cell excretion taken as 500,000 per 12 hours) occurred only six times in thirty-eight determinations. In each instance it was mild in degree, and when counts were repeated (on 2 patients) the hematuria was found not to be persistent. The clinical differentiation of renal inflammation of glomerulonephritis and renal passive congestion of hypertensive heart failure is often most difficult and occasionally quite impossible. In both instances there may be hypertension, cardiac enlargement, edema and moderate rise in the blood urea nitrogen. A qualitative analysis of a casual or 24-hour urine specimen may leave one with the impression that both sediments are of similar character in regard to formed element content. (Table 2.) However, a quantitative study of the urine sediment, as we have shown, will reveal the presence or absence of microscopic hematuria. While it is true that occasionally one sees glomerulonephritis without demonstrable microscopic hematuria, it must be remembered that the urine sediment count is not of itself diagnostic, but rather added fact which must be considered in the light of other correlated clinical data.

Table 5 represents a series of 31 patients with acute rheumatic infection investigated with the urine sediment count.<sup>4</sup>

TABLE 6.—STUDY OF THE TWELVE-HOUR EXCRETION RATE OF FORMED ELEMENTS IN THE URINE OF PATIENTS WITH SUBACUTE BACTERIAL ENDOCARDITIS.

Name.	No.	Date.	Urine volume, cc.	pH.	Specific gravity.	Protein, mg. per 12 hrs.	R. B. C. in millions per 12 hrs.	White and epithelial cells in millions per 12 hrs.	Casts per twelve hours, in thousands.					
									Total.	Hyalin.	Granular.	W. B. C.	Blood.	Temperature, °F.
Ca	1	5/29/30	514	5.0	1.020	277	18	4.24	3198	240	2958.0	0 0	0 0	103.0
Cb	2	5/17/30	420	5.0	1.020	453	52.92	5.04	151	151	0.0	0 0	0 0	100.0
E	3	1/3/30	131	5.0	1.027	28	0.56	0.56	12	8	2.1	2.1	0 0	103.0
H	4	1/18/30	410	5.5	1.014	410	44.28	3.69	273	273	0 0	0 0	0 0	101.6
K	5	1/15/30	309	5.5	1.016	411	68.36	23.64	103	0	28 0	75 0	0 0	101.6
		1/20/30	390	5.0	1.015	250	9.24	12.84	542	195	195 0	152.0	0.0	101.0
T	6	1/15/30	1180	5.0	1.014	629	11.51	5.55	277	179	33 0	65 0	0.0	100.8
		6/12/30	1340	5.5	1.007	578	24.34	4.65	74	74	0 0	0 0	0 0	
W	7	9/29/30	364	5.0	1.024	915	5.09	3.39	222	222	0.2	0 0	0 0	
K	8	9/12/30	804	6.5	1.017	184	142.31	11.26	279	179	0.0	75.0	25 0	

Table 6 shows the same observation in 8 patients with proven subacute bacterial endocarditis. Again a striking difference is noted, only in the degree of microscopic hematuria. Not infrequently the differential diagnosis between acute rheumatic endocarditis and subacute bacterial endocarditis is difficult at certain stages of the disease. It appears from our observations that the occurrence of persistent and well-marked microscopic hematuria along with the other clinical manifestations favors the latter diagnosis. The

occurrence of hematuria in subacute bacterial endocarditis is well known, and frank renal bleeding which may occur even in the absence of visible embolic phenomena, is highly suggestive of the diagnosis. However, the recognition of moderate degrees of microscopic hematuria which, if persistent, are just as significant, are often extremely difficult of recognition unless one resorts to an actual quantitative estimation.

**Summary.** The method for performing the urine sediment count (Addis) has been described in groups of: (1) "Normal" individuals (45); (2) patients with nephritis (10); (3) patients with congestive heart failure (26); (4) patients with acute rheumatic fever (23); (5) patients with subacute bacterial endocarditis (8).

The advantage in certain instances of a quantitative study of the formed elements in the urine sediment over the usual qualitative method of study has been indicated. It has been shown that the application of this more exact quantitative procedure may be of aid in making certain differential diagnoses.

**Conclusions.** 1. Healthy individuals in a 12-hour period may excrete up to 500,000 red blood cells, 1,000,000 white and epithelial cells and 5000 casts.

2. "Hematuria" is unusual as a result of renal passive congestion alone.

3. Subacute bacterial endocarditis is the only form of heart disease in which striking hematuria may occur.

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## DISTURBANCES IN HANDWRITING AND CLUMSINESS AS SIGNS OF TOXIC GOITER.

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At a recent medical meeting a statement was made by a nationally known neurologist that tremor of toxic goiter does not affect one's handwriting. This statement surprised me in view of my own

observations and studies of this phase of tremor of thyrotoxic origin. I found a similar, but somewhat modified statement by Jackson:<sup>1</sup> "The tremor is so fine that it does not materially affect the handwriting or cause a patient to spill a glass of water."

In obtaining a history 3 or 4 years ago from a patient at the time definitely toxic, a statement was volunteered that his first observation of anything wrong was in having trouble with the handwriting. While this was only an expression of tremor of the fingers and

Mrs. Isaac Lautenbach  
2312 Eastern Ave. S.E.  
January 21, 1928

Mrs. Isaac Lautenbach  
312 Eastern Ave S.E.  
January 12, 1931

Viola M. Sears  
Vernonville  
Michigan  
Nashville  
August 31, 1927

Mrs. Viola M. Sears  
Nashville  
Michigan  
R2  
September 22, 1927

Mrs. Burton Saur  
Sparta  
R.R. 4 Mich.  
July 15, 1928

Frank Duffy

Caenovia Mich.  
April 3, 1920

Frank Duffy

Caenovia Mich.  
June 2, 1928

Mrs. Gotschma  
Grand Rapids  
Mich.  
August 30, 1927

Mrs. Gotschma  
Grand Rapids  
Mich.  
October 13, 1927

Mrs. Burton Saur  
Sparta  
R.R. 4 Mich.  
November 14, 1928

The handwriting of 5 cases of toxic goiter before and after surgical treatment.

hands, it nevertheless was interesting. Other toxic goiter patients were then asked if there was any disturbance in their handwriting, and it was quite surprising to note how many had been so troubled. A number of specimens of handwriting were then gathered, both before and after their surgical treatment. (See illus.) They demonstrated that the handwriting may be very definitely affected as a result of the tremor that is a part of their toxicity. One patient volunteered the statement that the first intimation of a change in

his condition was that he observed some difficulty in shaving because of the tremor of his hands, a similar manifestation, of course. Jackson's reference to not spilling a glass of water further interested me because it is at variance with my experience. Patients have voluntarily mentioned being "clumsy." They drop their glasses, or dishes, or anything they may be handling.

Tremor is known to be one of the cardinal symptoms and signs of Graves' disease. It is also one of the earliest. It may be present for months before the disease is fully developed. The sign may first manifest itself as interference with fine work, as, for example, a woman doing needlework, or an artisan performing whatever kind of work in which he may be engaged. In other words, it is obvious that the tremor would be observed, if at all, by one doing fine work. Why should not tremor also affect one's handwriting? Tremor is, of course, not pathognomonic of Graves' disease, since it is also found in various other conditions, both functional and organic. The purpose of this note is not to discuss the entire subject of tremor, but merely to show that disturbances in handwriting, also "clumsiness," may obtain in goiter toxicity, when, if recognized, they may be the hint of the existence of an early or mild case of Graves' disease.

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### THE RELATION OF BROCA'S CENTER TO LEFTHANDEDNESS.

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THE question of an intimate connection between righthandedness and the localization of speech has found ample consideration in the literature, varying from merely statistical observations to highly speculative considerations.

Recently 2 cases have come under my observation which present several very interesting features.

**Case Reports.** CASE 1.—A young chemist came to my office complaining that the "stammering" from which he has been suffering for a number of years, has increased lately. On examination I find the heart slightly enlarged to the left and downward. Blood chemistry shows normal findings. Abdominal reflexes cannot be elicited. All tendon reflexes are more marked on the left than on the right side. The right pupil is slightly larger than the left, the right eyeground shows marked pigmentation in

its temporal half and the suspicion of a slightly choked disk. This patient has apparently, at one time or other, suffered an insult to his right hemisphere, possibly of an embolic nature. He is righthanded. Although suffering from an insult to his right hemisphere, his speech has become affected in the sense of paraphasia and paraphrapia. When talking he omits syllables and especially endings of words. When writing he leaves out parts of words and again especially endings.

CASE 2.—I am at present treating a man suffering with postencephalitis, with a clinical picture typical for this disease. The tremors, however, are confined to his left hand. This peculiarity may be explained by the fact that he is lefthanded. Yet his parents as well as his brothers and sisters are all righthanded.

A few months ago his mother, who is righthanded, suffered an apoplectic insult, with paralysis of the left half of her body. At the same time she was unable to speak. In other words, a hemorrhage to the right side of the brain in this case caused aphasia.

In a recent study Riese<sup>1</sup> remarks that occasionally in the course of inheritance a complete righthander or lefthander may transmit to his children only "decidedness" of a certain brain territory and not of a whole hemisphere, which would give cause to incomplete "seitigkeitsanlagen" of the brain. He notes that an occasional person may be a righthander and yet may possess in the right hemisphere, which is generally considered inferior, certain superiorities, as, for instance, the control of speech.

Bethe<sup>2</sup> emphasizes that only a few individuals show a primary preference for the right hand and that the final preference for the right hand is due to exogenous influences. He finds that among younger children the percentage of distinctly righthanded or lefthanded individuals is the same for the two hands, while in a group of older children there are three times as many righthanders as there are lefthanders. These findings coincide with those by Kistler,<sup>3</sup> who, besides, finds that every fourth child and every eighth adult is lefthanded.

Bethe further concludes that righthandedness and the predominance of the left hemisphere stand in only loose and indirect connection. In his opinion there is no reason why the fact that the preference for one hand may develop the opposite hemisphere should be carried over to a combination of movements as bilateral as speech. He believes that the localization of the speech center on one side is more a congenital factor than is the case with other motor centers which may be affected by the practice of monolateral movements.

In Case 1, we may well assume that Broca's center is located in the right hemisphere. Yet this patient is righthanded and has always been so, no effort having been made on the part of his parents to correct this "abnormality." This is demonstrated by the fact that, while both parents are righthanded, 2 of their 8 children have always been lefthanders. Nobody else in the family shows any difficulty of speech. There is a definite probability that in



1 of the parents or at least in 1 of the antecedents Broca's center is also located in the right hemisphere. The case shows that in the course of inheritance characteristics of not a whole side of a brain, but of parts of one hemisphere, may be transmitted separately.

In Case 2, a son is the only lefthander in the whole family. But when his mother suffers an apoplectic insult to the right hemisphere her speech becomes affected. This means that in this woman righthandedness has been completely compatible with location of Broca's center in the right half of the cerebrum. Yet, in 1 child of hers the connection between speech center and preference for one side (for some reason thus far unexplained) has become so intrinsic that this child is lefthanded. Here again, we may assume that among the antecedents there were some with the "abnormality" of rightsided Broca's center and others with lefthandedness.

Statistical surveys show a primary ambidexterity in spite of the prevalence of leftsided speech centers. Dextriposition may be more frequent than we generally assume. In 2 practical cases we have tried to show that this transposition bears no fundamental and intrinsic relation to the preference for the use of one or the other side of the body. It may, however, be that in some cases the location of the speech center on the right side is combined with a fundamental preponderance of the whole motor sphere of this side. Then we would have a case of clear leftsidedness from fundamental causes.

**Summary.** 1. Location of speech center and preference for one side of the body stand in only loose connection.

2. Location of Broca's center in the right hemisphere is compatible with righthandedness.

3. Description of 2 such cases, discovered following apoplectic insults, is herewith presented.

4. In both cases there are lefthanders and righthanders in the family. A combination of both "scitigkeitsanlagen" produces true leftsidedness.

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## REVIEWS.

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**SURGERY: ITS PRINCIPLES AND PRACTICE.** By ASTLEY PASTON COOPER ASHHURST, A.B., M.D., F.A.C.S. Professor of Clinical Surgery in the University of Pennsylvania. Pp. 1189; 1063 illustrations. Fourth edition thoroughly revised. Philadelphia: Lea & Febiger, 1931. Price, \$10.00.

"So much that is of real interest has been added to our knowledge of surgery in the last couple of years, that instead of being able to reduce the total number of pages by thirty, as was done in the previous edition, it has now been necessary to increase the total number by five.

"Among the new matter introduced, or the sections which have been entirely rewritten or which have undergone more extensive revision than the rest of the book, may be mentioned giant-cell tumors; rectal and spinal anesthesia; contusions of bone; mycotic aneurysms, symmetrical gangrene, thrombo-angiitis obliterans, injection treatment of varicose veins; the osteochondritides, scoliosis, coxa vara; compression of the brain; the Bovie electrosurgical apparatus; hyperthyroidism; trans-illumination of the mammary gland; gastric and duodenal ulcers, cholelithiasis and gall-stone formation; and tumors of the sympathetic nervous system. There have been introduced in all 49 new illustrations (all original), of which 33 are replacements of former illustrations supplied as the opportunities arose to secure better materials; and 16 are entirely new, no originals of which were formerly available. There remain now scarcely any illustrations (except a few diagrams) in the book which are not original. . . .

"In the present work emphasis is placed on the underlying principles, and pathogenesis, diagnosis, and indications for treatment have received particular attention. Descriptions of operations, however, have not been slighted. The more important operations have been described in detail, and in every case an attempt has been made to present clearly, if briefly, at least one method of operative procedure. The specialties of the Eye, the Ear, the Nose, and the Throat naturally are not included; and Genito-urinary Surgery, Gynecology, and Orthopedies have been discussed only so far as they come within the province of the general surgeon."

(FROM AUTHOR'S PREFACE.)

THOMAS SAY. *EARLY AMERICAN NATURALIST*. By HARRY B. WEISS, and GRACE M. ZIEGLER. A Foreword by L. O. HOWARD. Pp. 260; illustrated. Springfield, Illinois: Charles C Thomas, 1931. Price, \$5.00.

THOMAS SAY, "The Father of American Zoölogy," had several contacts with early American medicine. Descended from a Huguenot family long-resident in Pennsylvania, his father, Benjamin Say, studied drugs and medicine under the apprentice system then in vogue to become a successful physician-apothecary. He was prominent in several lines of civic activity and was chosen one of the Junior Fellows of the College of Physicians on its foundation in 1787, the year in which Thomas was born. Thomas himself was established by his father in the drug business in the firm of Speakman and Say, but their impractical habit fortunately soon produced failure, and allowed him to devote himself entirely to natural history.

A collecting trip to Florida and two others to the West, together with local expeditions in New Jersey and Pennsylvania, furnished material for many communications to the Academy of Natural Sciences and in 1824 for his pioneer book on American Entomology. Like his father, he had manifold interests. The Philosophical Society, the First City Troop on active service, Wistar Parties and such like afford the authors good opportunity for portraying early 19th century life in what was still the metropolis of the country.

The curious community experiment at New Harmony, Indiana, where Say spent his last decade until his death in 1834, and the evidence justifying the use of the opening term of this Review will be found in the later chapters composing the bulk of the book. Through the medium of a carefully portrayed individual life, a vivid picture of early American natural history and one of its chief pioneer, emerges.

E. K.

LEONARDO DA VINCI. *THE ANATOMIST*. CARNEGIE INSTITUTION OF WASHINGTON, PUBLICATION No. 411. By J. PLAYFAIR McMURRICH, Professor of Anatomy and Dean of the School of Graduate Studies, University of Toronto, with a Preface by GEORGE SARTON. Pp. 262; 89 illustrations. Baltimore: The Williams & Wilkins Company, 1930. Price, \$6.00.

By many considered as one of the greatest men who ever lived, by all acknowledged to be one of the outstanding figures in an age prolific in geniuses, one of the very few to attain top rank in several fields of human endeavor, and yet with important phases of his life only recently unveiled or still shrouded in mystery, Leonardo presents a complex problem to a biographer. From the time that Dalton, the librarian of George III, burst the lock of the chest that

contained the precious manuscript buried for more than two centuries, the artist of the Last Supper and of the smile of Monna Lisa, the engineer and architect of the Milanese, the sculptor of the heroic bronze of Ludovico Sforza, the eminent botanist, zoölogist and agriculturist has awaited adequate treatment from the point of view of medical history. It was a fortunate suggestion of Dr. Sarton's, ten years ago, that secured for this purpose the services of "one in whom the technical and the historical, the scientific and the artistic qualifications" were so generously developed and nicely balanced.

While the author, himself an anatomist of note, attempts to evaluate only one of his subject's many activities, he has fortunately been led much further afield in his recognition of the need of a proper perspective for this survey. Though he presents his evidence in a dispassionate, analytic manner, the reader is forced to agree with the warmer words of Vasari, that Leonardo gave "*veramente luce all'anatomia fino a quel tempo involta in molte e grandissime tenebre di ignoranza.*"

The numerous excellent reproductions of Leonardo's anatomical drawings, especially where the artistic touch was of major importance, conclusively show his ability, to observe accurately and independently. Some, however, and especially statements in his mirror-writing text, show his dependence on the Arabs even when it necessitates contradiction of the evidence of his own drawing. Thus we can agree with Sarton that, genius though he undoubtedly was, Leonardo belonged to his century as completely as many of his humbler contemporaries and that "This father of modern science was still in many respects a child of the Middle Ages."

E. K.

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A SYSTEM OF BACTERIOLOGY IN RELATION TO MEDICINE, VOL. 7, VIRUS DISEASES, BACTERIOPHAGE. By various Authors. Pp. 509; illustrated. London: Medical Research Council, 1930. Obtainable in the United States at British Library of Information, 5 E. 45th St., New York. Price, £1/1/9 for this volume; for the set £8/14/9.

IN the present volume of this great British System of Bacteriology is presented a thoroughly modern account of the important virus diseases and of the bacteriophage. The twenty-seven authors of the treatise are investigators of international reputation. The book begins with introductory chapters on viruses and virus diseases. The chapters following deal with individual virus diseases, such as smallpox, typhus, epidemic encephalitis, rabies, trachoma, warts, measles, leukemia of fowls, yellow fever, and so forth. The general treatment of the various diseases may be illustrated by citing the subjects discussed under lethargic encephalitis: history, sympto-

matology, pathology, comparative pathology, bacteriology, immunity, histology of experimental encephalitis in the rabbit, relationship of the virus of herpes febrilis to the etiology of encephalitis lethargica, summary, literature. The bibliography is excellent; the various authors have selected the more important contributions, and avoided unwieldily unnecessary repetition. The concluding chapter on bacteriophage and cognate phenomena is particularly noteworthy and represents a splendid review of our present-day knowledge. The entire work is thoroughly readable. Workers in the fields of pathology, bacteriology, immunology and the related sciences owe a debt of gratitude to the Medical Research Council of Great Britain under whose auspices the work has been prepared.

B. L.

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SIR D'ARCY POWER. *SELECTED WRITINGS 1877-1930*. Anonymous. Pp. 368; illustrated. Oxford: Clarendon Press, 1931. Price, 25s. net.

A CHARMING series of 16 articles from the pen of an internationally prominent writer on surgery and medical history—given him by his friends on the occasion of his 75th birthday. It is only unfortunate that limitations of space prevented a fuller selection from the copious storehouse indicated in the 609 articles listed in his bibliography. The 26 illustrations are models to the medical publisher in their interest and freshness to the casual reader. While Harvey, John Hunter and St. Bartholomew's naturally occupy the foreground, the interesting topics range from English medicine in the fourteenth century to "Imaginary Annals of the Section of Comparative Medicine." We congratulate both the author and his editorial friends on this delightful volume.

E. K.

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TREATMENT IN GENERAL PRACTICE. By HARRY BECKMAN, M.D., Professor of Pharmacology, Marquette University Medical School, Milwaukee, Wisconsin. Pp. 899. Philadelphia: W. B. Saunders Company, 1930. Price, \$10.00.

"THE neglect of thorough and painstaking teaching of therapeutics in this country;" the presentation in most medical schools of "a ridiculously inadequate course of lectures, usually to junior students who have had as yet practically no contact with the sick," the rest being left to the teachers in the department of medicine and the specialties who in the huge task of teaching the methodology of diagnosis have "no time left for an exhaustive consideration of the treatment of disease;" the consequent inadequacy of the average young practitioner's therapeutic knowledge: these are the author's reasons for writing this book.

There are described the treatments of the principal diseases of man, including most of those usually found in a textbook on medicine; also of certain genito-urinary affections; common diseases of the skin; burns; some obstetrical conditions. In each instance there is an introductory definition of the disease, and when indicated, a brief statement of the underlying pathology. In discussing treatment the author refers constantly to original sources (there are 32 pages of bibliography) with extensive quotations (there is 1 of 10 consecutive pages), well selected and with much good editorial comment by the author. One might quibble over some classifications: for example, malaria and sprue under "infections," or herpes zoster as a skin disease; and over some omissions (Banti's syndrome) and inclusions (ainhum). Few will share the author's enthusiasm for synthaline or will agree with his statement that enzymes will reappear in gastric achylia if enough acid is administered; or that allergy is really only a form of alkalosis (the Reviewer failed utterly to relieve hay fever patients by giving them nitrohydrochloric acid); or that the Christmas Seal educational campaign had little to do with the lowering of the death rate from tuberculosis (yet he admits elsewhere that "volume of organisms" is an important factor in determining the severity of all infections). We thought that most medical historians had exonerated Columbus' crew of the charge of introducing syphilis into Europe (Sudhoff, Karl: *Arch. de med., cir. y espec.*, 1929, 31, 5). But after all, these are minor criticisms and the Reviewer hastens to counterbalance them by assuring practitioners that they will find in this book an exceedingly useful, convenient and interesting addition to their library. R. K.

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THE METABOLISM OF TUMORS. Edited by OTTO WARBURG, Kaiser Wilhelm Institute for Biology, Berlin-Dahlem. Translated from the German edition, with accounts of additional recent researches by FRANK DICKENS, M.A., PH.D., Whole-time worker for the Medical Research Council at the Courtauld Institute of Biochemistry, Middlesex Hospital, London. Pp. 327; illustrated. New York: Richard R. Smith, Inc., 1931. Price, \$12.00.

DURING the course of investigations upon the respiration of sea-urchin eggs Warburg observed that at the moment of fertilization oxygen utilization was tremendously increased. Attributing this increased oxygen uptake to a corresponding increase in the growth rate, he felt that application of the same method of study to other rapidly growing cells, namely, tumor cells, might show a similar magnitude of oxygen consumption. To his surprise he found that tumor cells, especially the cells of malignant tumors, consumed

comparatively little oxygen. A repetition of the experiment was made and to the special Ringer's solution in which the determinations were made, was added glucose. It was then observed that oxygen consumption was not increased. On the other hand the tumor tissue produced large quantities of lactic acid from the glucose, both in the presence and in the absence of oxygen. This was very different from the behavior of normal tissue, which produced very little if any lactic acid when oxygen was present, and much less than tumor tissue in the absence of oxygen.

These important observations were published in 1923. Before that time very little was known of the metabolism of the cancer cell or of its relation to normal body cells. In the interval many observations have been made and an entirely new mode of investigation into the nature of tumor growth has been developed.

The collected papers from Professor Warburg's laboratory were published first in German in 1926. The present volume in English will enable those interested in the cancer problem to follow through translations of the original papers the development of this work. The English edition has included several papers issued after the publication of the German edition, among these Professor Warburg's most recent paper (1929) in which he sets forth his theory as to the cause of tumor growth.

It is his opinion that if the ability of growing cells to use oxygen is injured in any way the cells that survive will be those that can derive their energy by glycolytic rather than by the ordinary oxidative processes. These cells, continuing to grow in this extraordinary way, will thus become tumor cells.

To those who may wish to use the Warburg technique for the study of cell metabolism it will be a great advantage to have the original directions, descriptions of apparatus and so forth in English.  
E. W.

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THE DEVELOPMENT OF PHYSIOLOGIC CHEMISTRY IN THE UNITED STATES. By RUSSELL H. CHITTENDEN, Professor of Physiological Chemistry in the Sheffield Scientific School of Yale University 1882-1922. Pp. 427. New York: The Chemical Catalog Company, Inc., 1930. Price, \$4.50.

THIS valuable story of the development of biochemistry in this country, written by the dean of the American authorities on the subject, who has himself contributed much pioneer work in this field, shows "by explicit statements of actual experimental accomplishments, at different times and in different places, by many workers and groups of workers, something of the progress which has been made in this country during the past half century in the field of physiologic chemistry." It is one of a series of scientific and

technologic monographs published by the American Chemical Society, by arrangement with the Interallied Conference of Pure and Applied Chemistry, which met in London and Brussels in 1919.

No less truly historical than writings in other fields of biology that must perforce devote space to archaic ideas and methods, this book is able, while preserving the chronologic method of approach, to present a fair survey of the present status of biochemistry in many fields and a "suggestive outlook for the achievements of tomorrow." Where most of the contributions described have been by investigators who are living, the author has wisely abstained from critical analysis of the work or criticism, *pro* or *con*, of the workers.

Starting with the foundation of "the first physiologic laboratory for the use of students in the United States" by Bowditch at Harvard in the early seventies, the author, whose life study of the subject itself began in 1878, traces in the first 3 chapters the early general development of the subject in his country. The subsequent 9 chapters take up such topics as the study of proteins, the blood as a physico-chemical system, antiketogenesis, lipoids, anaphylaxis, oxidation reduction systems, vitamins, internal secretions, the chemistry of the brain and of the tubercle bacillus.

Consideration of the development of the specialty in such institutions as Columbia, the Universities of Pennsylvania and Michigan, the Mayo Foundation and a number of other institutions, permits inclusion of many valuable and interesting biographic details. With pardonable pride, the author brings out the important part played by the laboratory of physiologic chemistry at Yale, both as a center for research and in the number of students sent to important posts throughout the country.

We congratulate the American Chemical Society on this successful addition to American chemical literature "without primary regard to commercial considerations."

E. K.

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THROUGH THE ALIMENTARY CANAL WITH GUN AND CAMERA. Personally Conducted by GEORGE S. CHAPPELL. With an Introduction by ROBERT BENCHLEY. Pp. 231; 18 illustrations. New York: Frederick A. Stokes Company, 1930. Price, \$2.00.

A BIT of humor now and then is relished by the wisest men and the author, friend of the gallant Traprock and the famous square egged fatuliva bird, furnishes plenty in this venturesome journey through the "abominable regions." As Robert Benchley says, the "book ought to cause quite a stir in digestive circles." Among the illustrations, I prefer "My Castle on the River Bile."

E. K.



## BOOKS RECEIVED.

### NEW BOOKS.

- International Studies. Prevention and Treatment of Disease.* Conducted for The Milbank Memorial Fund by SIR ARTHUR NEWSHOLME, K.C.B., M.D., F.R.C.P. Vol. I. *The Netherlands, Scandinavia, Germany, Austria, Switzerland.* Pp. 248. Baltimore: The Williams & Wilkins Company, 1931.
- Text Book of Physical Therapy, Vol. I.* By WILLIAM BENHAM SNOW. Pp. 708; 183 illustrations. New York: Scientific Authors' Publishing Company, 1931. Price, \$10.00.
- Harper's Medical Monographs. Vols. I and II. Treatment of Injury.* By CLAY RAY MURRAY, M.D., F.A.C.S., Assistant Professor of Surgery, College of Physicians and Surgeons, Columbia University. Pp. 412; 196 illustrations. New York: Harper & Brothers, 1931. Price, 2 vols., \$5.00.
- Chemistry for Nurses.* By HARRY C. BIDDLE, A.M., Instructor in Chemistry, School of Nursing, Western Reserve University. Pp. 336; 74 illustrations. Philadelphia: F. A. Davis Company, 1931. Price, \$2.75.
- Collected Reprints from the Laboratories of the Mount Sinai Hospital, New York, 1930.*
- Medizinische Praxis. Band XII. Herz- und Kreislauf-Insuffizienz.* By DR. K. F. WENCKEBACH, Em. Vorstand der I. Medizinischen Universitätsklinik, Wien. Pp. 120; 7 illustrations. Leipzig: Theodor Steinkopff, 1931. Price, geheftet RM 8.00, gebunden RM 9.50.
- Peptic Uleer. A Symposium of the Current Literature.* Pp. 78; 8 illustrations. New Haven: The BiSoDol Company, 1931.
- The Renal Lesion in Bright's Disease.* By THOMAS ADDIS, Professor of Medicine, Stanford University, and JEAN OLIVER, Professor of Pathology, Long Island College of Medicine, formerly Professor of Pathology, Stanford University. Pp. 628; 170 full-page plates, 2 in color; 21 illustrations and 1 folding table. New York: Paul B. Hoeber, Inc., 1931. Price, \$16.00.
- The International Medical Annual. Forty-ninth Year, 1931.* Pp. 551; 53 illustrations, 70 plates. New York: William Wood & Co. 1931. Price, \$6.00.
- The Surgical Clinics of North America. Vol. II, No. 2 (Lahey Clinic Number, April, 1931).* Pp. 248; 88 illustrations. Philadelphia: W. B. Saunders Company, 1931.
- Trabajos y Publicaciones de la Clinica del Professor Pedro Escudero, Vol. Cuarto, 1930.* Buenos Aires: Pedro Garcia, 1930.
- Geneeskundige Kunstkalender Voor Heb Jaar 1931.* 25 illustrations. The Hague: J. Philip Kruseman. Price, \$1.50.
- Noguchi.* By GUS ECKSTEIN. Pp. 419; illustrated. New York: Harper & Brothers, 1931. Price, \$5.00.

- Rembrandt.* By DR. J. G. DE LINT. Pp. 113; 64 illustrations. The Hague: J. Philip Kruseman, 1931. Price, \$2.50.
- The Treatment of Asthma.* By A. H. DOUTHWAITE, M.D., F.R.C.P. (LOND.), Assistant Physician, Guy's Hospital. Pp. 164; New York: William Wood & Co., 1931. Price, \$2.50.
- On the Principle of Renal Function.* By GOSTA EKEHORN, M.L. Pp. 717; 60 illustrations. Stockholm: P. A. Norstedt & Soner, 1931.
- A Manual of Practical Vertebrate Morphology.* By J. T. SAUNDERS and S. M. MANTON. Pp. 220; 43 illustrations. New York: Oxford University Press, 1931. Price, \$5.00.

## NEW EDITIONS.

- Nutrition and Diet in Health and Disease.* By JAMES S. McLESTER, M.D., Professor of Medicine at the University of Alabama, Birmingham. Pp. 891. Second edition, revised and resct. Philadelphia: W. B. Saunders Company, 1931. Price, \$8.50.

The rapid recent advances in the science of nutrition have necessitated many changes since the first edition of this book. (See AM. J. MED. SCI., 1927, 176, 436.) Vitamins, diabetes, obesity, digestive disorders and even gout thus have required considerable modification and additions. Sections have been added on toxemias of pregnancy, colon and protozoan infections.

- Diagnostic Methods and Interpretations in Internal Medicine.* By SAMUEL A. LOEWENBURG, M.D., F.A.C.P., Associate Professor of Medicine, Jefferson Medical College. Pp. 1032; 547 illustrations. Second revised edition. Philadelphia: F. A. Davis Company, 1931. Price, \$10.00.

- Fundamentals of Dermatology.* By ALFRED SCHALEK, M.D., Professor of Dermatology and Syphilology, University of Nebraska College of Medicine. Pp. 247; 58 illustrations. Second edition thoroughly revised. Philadelphia: Lea & Febiger, 1931. Price, \$3.00.

Thoroughly revised and considerably enlarged, it covers the anatomy, physiology, symptomatology, diagnosis, prognosis and treatment of skin diseases in reasonably good manner in the limited space available.

- Clinical Diagnosis by Laboratory Methods.* By JAMES CAMPBELL TODD, PH.B., M.D., late Professor of Clinical Pathology, University of Colorado School of Medicine, and ARTHUR HAWLEY SANFORD, A.M., M.D., Professor of Clinical Pathology, University of Minnesota (The Mayo Foundation), Head of Section on Clinical Laboratories, Mayo Clinic. Pp. 765; 347 illustrations, 29 in colors. Seventh edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1931. Price, \$6.00.

This excellent manual, one of the best of its kind, should need no further introduction to medical readers. Dr. Sanford has upheld the high standard of previous editions. New methods for the culture of tubercle bacilli, determination of lead, precipitation of proteins from body fluids, blood sugar and uric acid, calcium, blood volume, use of histamin in gastric analyses, occult blood, Ascheim-Zondek test and others are included.

- Clinical Electrocardiography.* By SIR THOMAS LEWIS, M.D., F.R.S., D.Sc., LL.D., F.R.C.P., C.B.E., Physician of the Staff of the Medical Research Council; Physician in Charge of Department of Clinical Research, University College Hospital. Pp. 128; 107 illustrations. Fifth edition. London: Shaw & Sons, Ltd., 1931. Price, 8s 6d.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

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**The Relationship of Blood Uric Acid Content to the State of Renal Function in Nephritis.**—The blood urea clearance test has been found to be an extremely satisfactory method of estimating renal function (Moller, McIntosh and Van Slyke. The only difficulty with this method is that it is a trifle too complicated to be carried out as a common clinical procedure. However, as a method of comparing other renal function tests and determining their value and their worth in the laboratory, it is a procedure which seems to be the most accurate of any method used. The determination of uric acid concentration in the blood, with a simultaneous estimation of nonprotein nitrogen and creatinine, is a method which is very generally employed more or less routinely, often under the broad term of "blood chemistry." Medical men everywhere have the idea that the estimation of the waste products of nitrogenous metabolism in the circulating blood offers a practical method of determining the function of the kidney at any given time. High concentration of the uric acid is presumably definitely due to renal pathology. CHRISTOPHER JOHNSTON (*J. Clin. Invest.*, 1931, 9, 555) compares the urea clearance test with the concentration of uric acid in the blood. One hundred and seventeen tests were made on 30 patients, 21 of whom had chronic nephritis of the hemorrhagic type, 2 of whom had the acute hemorrhagic type of nephritis, 3 chronic degenerative, 3 arteriosclerotic, and the tests of 1 patient were carried out when he was in a condition of cardiac failure. The data that Johnston collected show that normal figures for blood uric acid occur in a very large number of nephritic cases, even with the urea excreting power being only 20 per cent of normal. Moderately increased blood

uric acid may be present when there is only slight renal damage or the most extreme loss of function. High blood uric acid figures occur only when the nephritis has attained an advanced degree, with the urea excreting power less than one-fifth of normal. This irregular correlation of blood uric acid to renal function, the author says, was to be anticipated, as uric acid is removed from the organism in part only by excretion. He concludes that the determination of blood uric acid as an indicator of renal function is of little value.

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**The Excretion of Intravenously Injected Bilirubin as a Test of Liver Function.**—HARROP, and GUZMAN BARRON (*J. Clin. Invest.*, 1931, 9, 577) write that the liver plays such an important rôle in the normal body that numerous methods have been advanced for the study of the functional efficiency of this organ. It has, however, more than one function and it is quite conceivable that dissociated functional disturbances may arise when the gland is acted upon by any noxious substance. Some of the functions are possibly more susceptible to the action of these injurious agents than others and among these there appears to be the inability of the liver to excrete bilirubin despite the fact that other functions of the liver are still unimpaired. The Van den Bergh reaction has been extensively employed to determine the degree of injury to the liver cells. It is assumed, however, that this particular reaction depends very largely upon extensive liver injury, as the factor of safety of this particular organ is very great. Certainly there exist many conditions of mild liver injury where bilirubinemia is not increased. The authors have made the basis of their study the concept that if an increased amount of bilirubin is injected into animal or man, insufficiency of liver may be demonstrated; assuming, as they bring out in their article, that evidence seems to indicate definitely that bilirubin is excreted *in toto* by the liver, that it is not retained by the cells of the reticulo-endothelial system, and that it is not excreted by the kidneys. They employed for their examinations bilirubin injections in dosage of 1 mg. per kilo of body weight in an alkaline solution, and the bilirubin of the blood was determined by the method of Ernst and Förster. They found in the normal individual the amount of bilirubin given above is excreted in from two to four hours, and in the majority of instances in three hours after the injection. Four hours they consider the maximum limit of the total excretion in normal individuals. The series of patients they studied were those in whom it was presumed that there was some slight disturbance of liver function, such as Rich and Resnik have observed in pernicious anemia and experimentally produced anemias. In this particular series of cases of anemia there was a definite retention of bilirubin at the end of four hours. In the second series, the patients were suffering from a variety of pathologic conditions, such as cirrhosis of the liver, postarsphenamin jaundice some months after clinical recovery, typhoid fever, and acute infectious diseases. It was found again in these diseases that there was a retention of this particular pigment. As a result of the study of this series of cases, the authors feel they are justified in concluding that "the bilirubin excretory power of the liver is the most delicate method so far proposed for testing the functional capacity of this organ."

## SURGERY

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UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

PHILADELPHIA, PA.

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**Peritonitis.**—MELONEY, HARVEY and JERN (*Arch. Surg.*, 1931, 22, 1) state that it cannot be too strongly emphasized that the most important prophylactic treatment for peritonitis, as seen in a general surgical hospital, is early diagnosis and early operation in acute appendicitis. A comparison of smear and culture with the pathologic condition at the time of operation gives a sound basis for prognosis. In the great majority of cases yielding bacteria in their series, there was a polymicrobial infection. In any specific prophylactic or active treatment for bacterial peritonitis, one must take into consideration the symbiosis of the commonest organisms found in the peritoneal exudate, namely, *Bacillus coli* and *Bacillus welchii*. The mortality in perforative cases was so much greater than in the nonperforative cases in their series that the rôle of the intestinal juices must not be forgotten. The results of this study lay the ground work and point the way to some specific experimental studies, of which may be mentioned: (a) vaccine and serum prophylactic and active treatment; (b) the bacteriostatic effect of peritoneal fluids; (c) the neutralization of digestive ferments, and (d) the synergisms and antagonisms of certain bacteria.

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**The Intervertebral Disks.**—SMITH (*Brit. J. Surg.*, 1931, 18, 385), says that the objects of the research, the results of which are given in this paper were to verify certain debatable points about the structure of the intervertebral disks and to determine the mode of nutrition, the state of the disks from infancy to old age and the diseases to which they are subject. The intervertebral disks are rudimentary diarthrodial joints possessing a cavity filled with villi, a fibrocartilaginous capsule, and upper and lower cartilaginous plates comparable to articular cartilages. The mode of nutrition is by blood channels, which pierce the cartilaginous plates from the marrow of the vertebral bodies. The disks allow a small degree of movement in all directions between the vertebrae and thus are highly important in imparting flexibility to the spine. They are also powerful buffers between the vertebrae, absorbing shocks transmitted along the spine. In the first two decades of life, an intervertebral disk is biconvex and highly elastic. The fibers of the annulus are fine and white, the cartilaginous plates thin, translucent and bluish white. In subsequent decades the disk tends to become progressively more coarse, inelastic, tough and discolored. The lesions of the disks which have up until now been described are fibrous, cartilaginous, calcareous, bony fatty, necrotic and liquefactive changes. Inflammatory changes are thought to be secondary to an affection of the spongiosa of the corpus vertebrae. In osteochondritis of the spine, the disks are affected as well as the vertebrae. There seems to be some reciprocal adaptability between the disks and the vertebrae

when either are diseased. Diagnosis of the lesions of the intervertebral disks depends on radiographic examination. Thinning and flattening, diminished transparency, peripheral or central calcification, obliteration by ossification or abnormal biconvexity, may be observed.

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**Transplantation of Ureters to the Sigmoid.**—SISK, WEAR and O'BRIEN (*Surg., Gynec. and Obst.*, 1931, 52, 212) claim that the transplantation of the ureters to the sigmoid in dogs is highly unsatisfactory by the Mayo technique. In every case the kidney became infected and closure of the uretero-sigmoidal opening by the mucosa of the bowel occurred in 5 of the 7 unilateral transplants. In the 2 bilateral transplants the ureteral openings were markedly stenosed. The completed Coffey technique gave slightly better results. Of the 8 dogs 4 showed bilateral infection, 3 showed infection on only one side and 1 showed no evidence of infection, but was hydronephrotic on one side. Complete closure of the ureteral opening occurred in only one ureter. The unilateral Coffey operations revealed kidneys in which there was no microscopic evidence of pyogenic infection, yet the dogs never appeared well after operation. Believing that the kidneys became infected by means other than the lumen of the ureter, the authors obtained infected kidneys in 2 cases in which the ureters were still completely obstructed at autopsy. The lymphatics must be given serious consideration as a means of transmitting infection to the kidneys. Solution of the problem of preventing ascending renal infection probably depends upon the discovery of means to prevent infection through the lymphatics. Partial success in this direction was obtained in experiments in which the authors tried to protect the exposed end of the ureter for a time from infected material. Until a uniformly successful procedure is evolved, it would seem the better surgical judgment to use ureteral transplant only in those cases in which older and better understood methods are impossible.

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**Experiences With the Cerebellar Astrocytomas.**—CUSHING (*Surg., Gynec. and Obst.*, 1931, 52, 129) says that the cerebellar astrocytomas furnish another example of gliomatous tumors which show predilection for a favorite site and produce a recognizable syndrome. The tumors are probably of congenital origin and usually date symptomatically from childhood, the average age on admission being thirteen years. They are signalized by period matutinal headache and vomiting owing to their midcerebellar situation, the tumors invariably cause secondary hydrocephalus and this in turn leads to a choked disk, which may be so insidious in origin that seriously impaired vision may be the first recorded symptom. They may attain a surprisingly large size before any cerebellar signs, usually shown as instability, put in an appearance. The clinical diagnosis lies between astrocytoma and other forms of tumor that frequent the same region, medulloblastoma, angioblastoma and ependymoma, of which the astrocytomata are the most numerous. The tumors may lie exposed on the surface, or be wholly concealed, and when so concealed a vertical invasion through the vermis is the proper method of bringing them into view.

## THERAPEUTICS

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UNDER THE CHARGE OF

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NEW YORK CITY,

AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL,  
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**Congo-red as a Hemostypticum.**—WEDERKIND, BECKER and WIENERT (*München. med. Wchnschr.*, 1930, p. 2049) injected intravenously 5 to 10 cc. of sterile 1 per cent solution of Congo-red in cases with bleeding. The result of this therapeutic measure in 19 cases in whom the bleeding was caused by pulmonary tuberculosis, bronchiectasis, menorrhagia, tooth extraction, duodenal ulcers and malignancy is reported. The authors claim that the bleeding stopped between one-half to six hours following the intravenous injection of the Congo-red; and present some evidence that Congo-red stimulates the reticulo-endothelial system, increases the blood platelets and the fibrinogen content of the blood.

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**Convalescent Serum in the Prophylactic Treatment of Measles.**—Serum or whole blood obtained from patients recovering from infectious diseases has repeatedly been used therapeutically. NABARRO and SIGNY (*Brit. Med. J.*, 1931, vol. 12) state that at present human convalescent serum is far more reliable than the available animal serum. The serum is obtained from adults suffering from measles. Each patient is carefully examined before bleeding and particular notice taken of any syphilitic or tuberculous taint. Between the seventh and the fourteenth days after defervescence, 200 to 300 cc. of blood are collected aseptically into sterile oxalate solution. The serum is separated after the oxalate is precipitated with calcium chlorid. If the sterility test and the Wassermann reaction are satisfactory, 0.5 per cent phenol is added and the serum then pooled with other sera so as to obtain a product of uniform potency. In order to achieve complete protection, the serum should be injected before the fifth or sixth day of incubation. This results in a passive immunity which lasts roughly a month. If injected from the sixth to the ninth day, the serum does not protect fully and a very mild attack of measles may ensue. No benefit can be expected from injection after the ninth day. The mild attack which follows the late administration of serum manifests itself in a temperature of 100° F., which appears about the fourteenth day of the incubation and lasts for a day or two. A few measly spots over the trunk and mild coryza may appear for a day or two. Koplik's spots are never observed. A disturbing aspect is the prolongation of the incubation period, which may last for twenty-six days. The

satisfactory dose is 5 to 7 cc. given intramuscularly into the buttock. The serum has no value in the treatment of severe cases of measles. In a series of 586 cases, of which 461 were hospital cases and 125 from private practice, failure was observed in 3 per cent and 5.6 per cent of the cases respectively, to whom prophylactic treatment was given. Several of the cases in which the treatment failed were injected after the fifth day.

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**Experiences With Symbiotic Serum in Diphtheria.**—Following the observations of Canon and Haaken on the frequency with which diphtheria was found to be combined with streptococcal infection, MEDEM (*Deutsch. med. Wchnschr.*, 1931, 57, 146) employed a stock polyvalent streptococcic serum in combination with diphtheria antitoxin in the treatment of a group of cases, but saw no significant benefit. By cultures from the membranes and from puncture of the inflamed cervical nodes, he was able to find, however, streptococci in at least 50 per cent of all cases. Believing that these streptococci were somewhat modified by their symbiosis with the diphtheria bacilli, he then began to employ a mixed serum prepared from cultures obtained from patients suffering from diphtheria. This combined or symbiotic serum represents an unconcentrated diphtheria antitoxin plus a streptococcus antiserum. Used in 50 cases of septic diphtheria, the results were most gratifying, only 2 of the 50 failing to recover, both of which were severely intoxicated and first seen on the fifth and sixth days respectively of their disease. Medem feels that it is too soon to speak positively as to the value of this symbiotic serum. He feels definitely that it has considerable promise of improving the treatment of diphtheria in its septic forms.

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**A Remarkably Active Liver Extract Which Produces a Beneficial Response in Pernicious Anemia and in Combined System Disease.**—In a previous abstract published in this column attention was called to Gänsslen's preparation of a liver extract which when injected intravenously in amounts of 1 to 2 cc. daily, corresponding to 5 to 10 gm. of fresh liver, resulted in a remission within ten to fifteen days in patients with pernicious anemia. SCHILLING (*Klin. Wchnschr.*, 1931, 10, 301) now confirms Gänsslen's claims and reports his experiences with special reference to the problems of "liver resistance" and combined system disease. The discussion centers on those patients with pernicious anemia in whom every other therapeutic measure failed after proper application, and additionally on a group of patients to whom, for various reasons, liver could not be administered successfully by mouth. Comparing his results with those from other extracts, Schilling affirms that Gänsslen's extract is not only a potent preparation but distinctly better than any other preparation in use. The efficacy of this extract is also shown by the fact that it produces a remission even in cases with such complications, in which other liver extracts failed. Schilling believes that the failure of orally administered extracts may be due to faulty absorption through the gastro-intestinal canal. He observes that patients with combined system disease show improvement following the injection of the Gänsslen extract. The degree of improvement is



similar to that observed after the oral administration of large amounts of raw liver in cases in which oral administration of liver extracts did not seem to benefit the patients. Schilling also observed considerable improvement in the general condition of his patients. The appearance and the turgor of the tissues improved. There was an increase in the capacity for work. It is noteworthy that improvement in the general condition of the patient was observed even in cases in which the blood findings had been brought to normal by liver therapy but with no improvement in the general condition. Such observations were made especially on elderly patients who continued to complain of paresthesias, mental depressions and lack of appetite, although their hemoglobin reached such high values as 90 to 100 per cent following daily doses of 250 gm. of liver. Schilling considers the Gänsslen extract a distinct advance in the liver therapy of pernicious anemia.

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## PEDIATRICS

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UNDER THE CHARGE OF

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**The Prevention of Rickets in Premature Infants by the Use of Viosterol 100-D.**—MAY (*J. Am. Med. Assn.*, 1931, 96, 1376) instituted this study in order to determine the dosage of viosterol for the prevention of rickets in premature children. It was soon apparent that there was a definite improvement in the weight, general well-being, hemoglobin concentration, calcium-phosphorus index and bone development in those infants constantly under supervision who received an adequate dose of viosterol, in contrast with those infants whose mothers were somewhat indifferent about following instructions as to the daily administration of viosterol, and the general care and feeding of the infant. Nearly every newborn infant is endowed with the amount of calcium and phosphorus in its body necessary to maintain a satisfactory balance until such time as adequate amounts are received through the mother's milk. This is especially true of the full-term infant. The artificially-fed baby may do well for many weeks without requiring an extra supply of vitamin D to keep up a normal calcium and phosphorus balance. On the other hand, the premature baby may be more susceptible to the development of a negative calcium-phosphorus balance on account of difficulty in ingesting enough milk, even by gavage, during the first few weeks of life. It is an accepted fact that premature infants are prone to develop rickets. They possess other physical inadequacies which directly or indirectly cause a high death rate in the first weeks of life. In respect to the high incidence of rickets, it does not seem to be entirely due to the inability of the infant to take sufficient milk, nor has it been established that a depletion of calcium and phosphorus necessarily occurs when the milk intake is subnormal. The relation of

intrinsic and available extrinsic calcium and phosphorus to their utilization after adequate administration of vitamin D is not well understood, and, until this biologic phenomenon is fully explained, exact procedures for the prevention of rickets cannot be planned. It is increasingly apparent that vitamin D in the form of viosterol is a vitally important factor early in life of those infants highly susceptible to rickets, and its judicious use from the first day of birth seems to increase the possibility of their survival and normal growth.

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**Chronic Stridor in Childhood, Sometimes Erroneously Attributed to Enlargement of the Thymus.**—KENNEDY and NEW (*J. Am. Med. Assn.* 1931, 96, 1286) says that the diagnosis of enlarged thymus is frequently made in cases in which further examination has disclosed other conditions as the cause of symptoms. Stridor, dyspnea, hoarseness, spells cyanosis and wheezy and noisy respiration can usually be accounted for on other bases than enlarged thymus. Laryngoscopic examination is often essential for definite diagnosis. Enlargement of the thymus can seldom, if ever, be established as a cause of death. Pre-operative examination and care of infants and children should be directed toward finding and correcting all conditions affecting surgical risk. Unjustified reports have caused the assumption that enlargement of the thymus accounts for much morbidity and mortality in infancy and childhood. The authors have not found it necessary to carry out pre-operative Roentgen therapy. They do give, however, a great deal of attention and pre-operative care to those children showing evidence of infection of the upper respiratory tract, fever, anemia, cardiac and renal disease, malnutrition, gastrointestinal disease and other conditions which might increase the operative risk.

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**On Enuresis.**—MANDEL (*Brit. J. Child. Dis.*, 1931, 28, 1) classifies the types of enuresis so as to make them clinically more easily recognized, and with a view of choosing the approved method of treatment which should be adopted. First there are those in which there is some physical irritant, such as worms, overdistention of the bladder, cystitis and the like. The hypersensitive, neuropathic or nervous type shows instability as the symptom which may be regarded as of importance equally with such symptoms as cyclic vomiting, ketonuria, vagotonia and the like. These respond to dietetic and medicinal treatment combined with readjustment of environment and reëducation. The so-called psychopathic child, in whom the enuresis is more a behavior complex, requires treatment directed toward the psychologic aspect. In endocrine disharmony, particularly hypothyroidism, there develops a loss of inhibition. Small doses of thyroid give results, especially if aided by the use of pituitrin for its tonic effect on unstriated muscle. A final cause is seen in the debilitated child. In such general tonic treatment gives results. In all cases atropin or belladonna is the specific drug.

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**A Syndrome Characterized by Congenital Clouding of the Cornea.**—HELMHOLTZ and HARRINGTON (*Am. J. Dis. Child.*, 1931, 41, 793) found that there were many references in the literature on cloudy swelling of the cornea, but that few definite cases are reported, and that most

of the discussion is in regards to the cause of the condition, about which there are different opinions. Some writers are convinced that the corneal lesion is noninflammatory, owing either to arrested development in early uterine life, which results in failure of the cornea to become transparent, or to a nutritional disturbance of some kind. Others are equally insistent that the lesion is due to intrauterine inflammation, and that it is secondary to inflammation of the entire uveal tract. They base their claims on pathologic examinations, and consider syphilis as the most common etiologic factor. It is rather difficult, however, to accept this, as syphilis is common and corneal clouding is rare, and also because of the absence of other syphilitic manifestations in these cases. Many cases of corneal clouding have cleared up within a few months after birth. In such cases it is believed that the condition is due to redundancy of aqueous humor rather than to arrested development. In the cases reported by the author there was no evidence of syphilis and no history to suggest early inflammation. They do not have an adequate explanation of the etiology. The most striking feature is the uniform cloudiness of the cornea. This along with other anomalies, places the condition in a special group, forming a clinical syndrome. The characteristic of the syndrome are the uniform cloudiness of the cornea; short, thick, clawlike hands and feet, with limited extension; restricted motion of the joints of the extremities; lumbar kyphosis; scaphocephalic head and mental retardation.

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**Acute Encephalitis During Childhood.**—HOLZMANN (*Deutsch. med. Wchnschr.*, 1931, 57, 144) states that because of the many clinical manifestations, the differential diagnosis of encephalitis is extremely difficult. Two cases of encephalitis in children are described. In a girl, aged 7 years, the clinical picture suggested a meningitis of tuberculous character. The spinal puncture did not corroborate this diagnosis, because the pressure was not abnormally high, the albumin reaction was negative and the cellular elements were not increased. It was found that the sugar content of the cerebrospinal fluid was extremely high, being 285 mg. per 100 cc. The normal sugar content of the cerebrospinal fluid ranges from 50 to 75 mg. per 100 cc., and in tuberculous meningitis the sugar content may even be lower. Several investigators have observed an increased sugar content in cases of encephalitis. This case was for that reason diagnosed as encephalitis. Clinical symptoms which suggested encephalitis rather than meningitis were the accelerated pulse and the leukoeytosis. The patient recovered completely, and with no nervous stigmata. The second patient was a boy, aged 3 years, who showed the symptoms of a hyperkinetic form of encephalitis. In this case also the spinal fluid was shown to contain excessive amounts of sugar but was free from albumin and showed no increase in the cellular elements. This patient died, but no necropsy was performed. The author feels that the increased sugar concentration of the cerebrospinal fluid is a valuable point in the differential diagnosis. That a high sugar concentration indicates an unfavorable prognosis was not corroborated by these observations. It seems that the sugar content is especially high in cases in which the respiratory disturbances are present. This is seen where inflammation of the medulla oblongata is especially pronounced.

## DERMATOLOGY AND SYPHILIS

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**Comparative Excretion and Absorption of Different Bismuth Products.**—HANZLIK and MEHRTENS (*Arch. Derm. and Syph.*, 1930, 22, 861), summarize their exhaustive studies on the clinical excretion of bismuth reported by the authors in the same and the two preceding numbers of the Archives of Dermatology, and in addition include a table of bismuth products with average bismuth content and a brief comparative résumé of absorptive studies in animals. The bismuth content in the products examined ranged from 20 to 75 per cent, but the authors believe that this factor is less important in the choice of a product than the criteria of vehicle, solubility, tolerance, absorption, and excretion. The adjustment of dosage can be made to compensate for variations in bismuth content. The following are a few of the more important conclusions: (1) A comparison of the clinical urinary excretion of bismuth during the first two weeks after the intramuscular injection of the different types of bismuth indicates that the water-soluble bismuth sodium tartrate, used in aqueous medium, was more efficiently absorbed than the insoluble products, used in oil or in aqueous medium (bismuth metal, potassium bismuth tartrate, and bismuth salicylate). (2) In general, increasing the dosage of bismuth products tends to diminish the total urinary excretion independent of the time factor and regardless of the bismuth product and the vehicle used. The cause of this is not understood, but certain possibilities are discussed. The phenomenon indicates the accumulation of bismuth in the body with increasing dosage. It is suggested that intensive medication and the use of total doses the equivalent of from 1 to 2.4 gm. of bismuth should be avoided. (3) The desirability of using small repeated doses instead of intensive medication for maintaining a uniform saturation of the tissues in the treatment for syphilis is suggested. (4) Generally, the results given in the literature indicate that the clinical use of different bismuth products in similar, equivalent doses of bismuth in lower therapeutic ranges (about 0.3 gm.) appear to give a similar total urinary excretion of bismuth, regardless of the bismuth product and the vehicle used. (5) The comparative total excretion of bismuth after the intramuscular injection of different bismuth products in different animals, as reported in the literature, is generally smaller than the clinical excretion, due apparently to the use of higher doses of bismuth; doses within the toxic fatal range showed smaller excretions than did those within the thera-

peutic range. Exact comparison of the different products was impossible on account of several variables affecting the results. (6) Collectively, the results given in the literature on the absorption of bismuth, obtained by the chemical analysis of tissues after the injection of different products of bismuth, indicate that all types of bismuth are well absorbed from the site of injection, regardless of the type or vehicle; the poorest absorption occurred with the insoluble products, used in oil or aqueous medium, and the greatest with soluble products, used in aqueous medium. Compared with the results on total excretion in animals, those on absorption showed an apparent lack of correlation; that is, much more bismuth would seem to be retained in the body according to the excretory results than according to those on absorption. After urinary excretion is completed, roughly one-half of the administered bismuth remains in the body to be gradually excreted over long periods in amounts too small to be detected. (7) The comparative fecal excretion of different bismuth products is similar and too small to account for the bismuth unaccounted for in urine. The median fecal excretion is about one-eighth of that in urine, indicating that the main channel of excretion is the kidney, which correlates with a high selective distribution of bismuth to this organ. (8) From considerations of clinical and animal results on excretion and absorption, and providing everything else is satisfactory, the choice of cationic bismuth products would appear to favor the water-soluble type, used in aqueous or tissue-soluble medium; this insures prompt and efficient tissue distribution and saturation, with corresponding antisypilitic efficiency. Insoluble products of bismuth and insoluble vehicles are objectionable for well-known reasons, although the absorption and excretion of bismuth may be as good as after the administration of soluble products. Improvements on the soluble bismuth products are desirable as regards the vehicle for administration (this may be achieved by the use of ethylene glycol), and as regards the choice of products for efficient penetration of the brain, those containing bismuth as anion appear promising.

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**Experimental Studies in Eczema.**—KLAUDER and BROWN (*Arch. Derm. and Syph.*, 1930, 22, 877), have studied the potassium, total and diffusible calcium ratios in the blood of 107 patients with 24 different diseases of the skin as a further elaboration of their animal experimental work showing that the ratio of calcium and potassium ions largely governs the degree of irritability of the skin. The authors preface their study with a summary of the work done on serum calcium in patients with dermatoses and review in detail the accepted functions of calcium in the body. They stress the point that an estimation of total serum calcium is no index of available calcium for it has been shown that only 50 to 70 per cent of blood calcium is in diffusible form, and that of this amount but 15 to 25 per cent is ionized. The authors selected for study those diseases of the skin in which the sympathetic nervous system is apparently concerned in the pathogenesis (that is, generalized pruritus, urticaria, angioneurotic edema, prurigo of Besnier), and calculated the percentage diffusible calcium of total calcium, the potassium-calcium ratio and the potassium-diffusible calcium ratio. The latter two ratios

were then correlated one with another and compared with the ratios obtained in normal persons and patients with other dermatoses. The following figures were regarded as normal: total serum calcium, 9 to 11; total serum potassium, 18 to 20; percentage of diffusible calcium of total calcium, from 45 to 55 per cent; potassium-calcium ratio up to 2.10; potassium-diffusible calcium ratio, from 3.50 to 4.50. The data presented show that the calcium and potassium range in patients with different dermatoses was generally normal. The abnormal ratios were rarely striking in character and were not constant in all cases of the disease under investigation. The prurigo of Besnier (diathetic eczema) gave the most abnormal ratios due to the greater decrease of diffusible calcium. In this condition 5 of 9 patients had an abnormally high potassium-calcium ratio and 7 of the 9 had abnormally high potassium-diffusible calcium ratios (below 4.50). Besnier's prurigo is a member of the asthma-eczema-hayfever group of allergic diseases and the authors believe is associated with abnormal functioning of the vegetative nervous system and endocrine dysfunction, especially hypoadrenia. A table is included showing the change from abnormally high ratios to normal ratios after the administration of sympathetico-tonic drugs (calcium, epinephrin, atropin, ultraviolet, codliver oil, diet), and the authors conclude that this type of therapy is indicated in some but not all patients with pruritus accompanied with neurosis, urticaria, dermatographism, and especially the prurigo of Besnier.

## GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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**Myomectomy.**—For 18 years BONNEY (*Lancet*, 1931, 220, 171) has been extending the possibilities of myomectomy, until now he feels that it is unusual to meet a case of fibroids, no matter how numerous the tumors, how large or how placed, that is beyond the scope of conservative surgery. During this period of his intensive work he has performed the operation 403 times. The tumors were solitary in 166 cases and multiple in 237 cases. The greatest number of fibroids he has removed from a single uterus is 125, and after this 92, 80, 55, 52, 48, 46 and 44, while on 28 occasions the number has varied between 15 and 30. Just as the number of tumors is no bar to the operation, neither is the size of the growth, as he has performed the operation where the total mass was about that of a full-term pregnancy. He emphasizes that the ease

or the difficulty of the operation depends less on the size and the number of tumors than on the position they occupy in the uterus. Thus a tumor on the lateral wall is more troublesome to remove than one on the anterior wall and a tumor in the posterior wall more difficult than either. There have been 7 deaths in the series, an operative mortality of 1.7 per cent. He was able to ascertain the present status of 210 cases, none of which had been operated upon less than 2 years previously. Of this group menorrhagia recurred in 10 cases, 5 of which subsequently required hysterectomy. In 8 cases new fibroids developed after the operation, but in 2 of these no further surgery was required. His experience makes him believe that the tendency to the formation of fibroids is a passing phase in the uterine tissues and not a continuous defect, otherwise myomectomy would be bound to fail in a very large proportion of the cases, whereas he has found recurrence quite rare. He believes that in most instances the nuclei of all the fibroids a woman is ever going to grow are laid down by the time she has reached 30 years or a little over. It follows that when myomectomy is performed on patients in the twenties or early thirties the fibroid-forming tendency has not yet gone into abeyance and the chance of the formation of new tumors is on this account considerably greater than when the operation is performed on patients over 34 years of age, especially when the number of tumors removed at the first operation has been considerable. On the other hand, it is in just these young patients that the desirability of saving the uterus is greatest, and if surgery can restore their marriage value for even a few years or enable them to have even one child, a great gain is effected, even if hysterectomy is necessary later. Of 77 patients in whom conception was desired 30, or 39 per cent, did conceive after myomectomy. In regard to the technique which he uses, it is interesting to note that a clamp is applied to the lower uterine body which compresses both uterine arteries at the same time. By this means, together with the application of ring forceps on each ovarian artery, all four main vessels are temporarily controlled, so that the field of operation will be practically bloodless and the operator can work deliberately without loss of blood and with the field of operation unobscured by hemorrhage. The uterine clamp is applied from the pubic end of the abdominal incision, and it is essential that the round ligaments should be included in its grip, otherwise the tightening causes it to slip down on the conical cervix until finally it is compressing the vagina below the uterine arteries. The clamp and forceps are not removed until the suturing of the uterus is completed. When they are taken off there is a certain amount of oozing from the suture holes, which soon ceases after the uterus is returned to its place. Whenever possible, the primary incision should be single and median through the anterior wall of the uterus in order to prevent adhesions to other intraperitoneal organs. Tumors not directly accessible through the median anterior incision are reached by secondary incisions made from the primary incision. In the majority of cases he believes that it is advisable to open and explore the uterine cavity in order not to miss a small submucous myoma or polypus, and thus, perhaps, leave behind the chief cause of the menorrhagia for which the operation is being performed. The opening of the uterine cavity will not increase the risk of the operation unless the uterus is already infected, in which

event myomectomy should never be attempted. Tumors of the posterior wall are often removed through this incision into the uterine cavity. Following the removal of large myomata, the remaining portion of the uterus must be reconstructed by trimming away superfluous tissue and by careful obliteration of the remaining cavities. For the latter purpose Bonney prefers tier sutures of catgut. His paper is concluded with a description of his various methods of dealing with unusual types of fibroids, which should be carefully read by those contemplating this type of surgery.

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## OTO-RHINO-LARYNGOLOGY

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UNDER THE CHARGE OF

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**Observations on Semon's Law. Derived from Evidences of Comparative Anatomy and Physiology.**—In masterful style, NEGUS (*J. Laryngol. and Otol.*, 1931, 46, 1) presents a scholarly, detailed and comprehensive contribution designed to unravel the history of the laryngeal muscles, to describe their functions, and to distinguish between the primitive and the more recently acquired duties. Stating that "the evidence of comparative anatomy is strongly in favor of its truth," the author takes as the basis of his discussion Semon's law. This law depends "on the proclivity of the abductor fibers of the recurrent laryngeal nerve to become affected sooner than the adductor fibers, or even exclusively, in cases of undoubted central or peripheral injury or disease to the roots or trunks of the pneumogastric, spinal accessory, or recurrent nerves." This observation demonstrates that if the recurrent laryngeal nerves, which supply the intrinsic are partially deranged in their function, the individual may be able to carry on movements of closure but not movements of dilatation on one or both sides of the larynx according to whether one or both nerves are affected. The outstanding factors in support of Semon's law are the observations that the sphincteric muscle band of the larynx serves a vital function, on which depends the very existence of the individual, and it is of more ancient origin than its antagonists—the dilators. Although admitting the limitations of his subject in the field of practical utility, Negus points out certain very important clinical adaptations—such as the possibility of death from asphyxia in bilateral paralysis of the abductor muscles; the value of estimating the alveolar  $\text{CO}_2$  or the alkali reserve of the blood as an index for surgical intervention; the prevention of posttracheotomy respiratory failure by the administration of  $\text{CO}_2$ .

**Relation of Infection of the Ear and Infection of Intestinal Tract in Infants.**—"Infection of the mastoid antrum is *not* the cause of acute intestinal intoxication in infants." Such is the conclusion of WISHART (*J. Am. Med. Assn.*, 1930, 95, 1084), the physician-in-chief and his



research department, and the pathologist and his department at the Hospital for Sick Children, Toronto. After an intensive, comprehensive and impartial study over a 5-year period, the medical staff of the above-mentioned hospital believes that the type of acute intestinal intoxication in infants is the same as that which exists in other parts of Canada and in the United States. It was found that a "cold" rarely attended the onset of the disease; that most of the infants showed no clinical manifestations of upper respiratory tract infection during the span of their toxicity; that there was no correlation between the bacteriologic findings of the upper respiratory and intestinal tracts; that many infants were free of otitic infection during the entire course of the illness; that the incidence of mastoiditis in these cases of acute intestinal intoxication is not high; that bilateral mastoidectomy as a cure for this condition was a failure; that a mastoidal operation is indicated only if an infant has typical signs of mastoiditis; that operation is not necessarily urgent, even in the presence of an acute streptococcic infection; and that operation is to be postponed as long as possible. Incorporated in the article is such a noteworthy statement as: "Our medical staff has now seen so many sufferers from this disease *with normal middle ears and mastoid antrums* that it refuses to allow the *mastoids of infants* with acute intestinal intoxication to be operated on unless they exhibit true clinical mastoiditis. Furthermore, it is stated that "Evidence is being accumulated to show that the disease (acute intestinal intoxication—Ed.) is of intestinal origin."

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## RADIOLOGY

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**Electrosurgical Destruction of Recurrent Lymphoid Tissue After Tonsillectomy.**—HOLLENDER (*Arch. Phys. Ther., Roentgen Ray, Radium*, 1930, 11, 600) points out that incomplete tonsillectomies are constantly being performed. Pieces of tonsillar tissue are found in the fossæ. The patients are usually victims of certain systemic infections, such as rheumatism, cardiac disease and nephritis. Repeated exacerbations of sore throat and tonsillitis are also common. Secondary removal by the dissection method is successful and finally leaves clean fossæ in a certain number of cases. In an equal number a further recurrence is observed. In this latter class surgery cannot again be entertained, and the author regards surgical diathermy as the ideal procedure. Electrodesiccation or electrocoagulation may be employed. If a large amount of tissue is to be destroyed electrocoagulation is preferable. For small masses of lymphoid tissue, electrodesiccation is the method

of choice. Gradual disappearance of the lymphoid mass can be observed at successive examinations. Too much tissue should not be destroyed at a single treatment, as the method calls for gradual destruction without severe reactions or discomfort.

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**The Value of the Roentgen Ray Examination in Pulmonary Tuberculosis.**—Next to the demonstration of tubercle bacilli in the sputum, characteristic Roentgen ray findings are the most positive evidence of pulmonary tuberculosis, according to RIGLER (*Minnesota Medicine*, 1930, 13, 25). A negative Roentgen ray examination is the best evidence against pulmonary tuberculosis that can be obtained. When symptoms of tuberculosis are present the Roentgen ray examination is almost always positive. Every patient with symptoms suggestive of pulmonary tuberculosis should have an adequate Roentgen ray examination, regardless of a negative physical examination. The Roentgen ray findings frequently do not indicate whether the tuberculous lesion is active; this may better be determined by the clinical signs. The roentgen examination gives an accurate picture of the extent and type of tuberculosis present. It is an invaluable aid in determining the type of therapy to be used, the effects of therapy and the course of the disease. Fluoroscopy is of little value in the diagnosis of early cases, and stereoscopic films are imperative.

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**Intravenous Urography and Uroselectan.**—Six cases in which intravenous urography was employed are described by LEWIS, CARROLL and SCHATTYN (*Radiologic Review*, 1930, 52, 337). The authors consider the method well adapted to patients so weak that they cannot bear instrumental ureteropyelography, and to those in which cystoscopy is impracticable for any reason. It is improbable that cystoscopic urography will ever be supplanted entirely by the intravenous. The writers have already met with cases in which they would have been misled completely if they had relied on uroselectan; on the other hand, the intravenous method has revealed important conditions that probably would have been overlooked by the retrograde method. It is therefore obvious that each has its sphere of usefulness and advantage. Observation of a considerable number of films indicates that the cystoscopic negatives are usually much clearer and more distinct than those made by the intravenous method. Their evidence is on the positive side while much of the intravenous evidence is on the negative side, which is by no means as direct and forceful as the positive.

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**Deep Roentgen Ray Therapy of Mammary Carcinoma—Five-year Results.**—From their study of 175 cases EVANS and LEUCETIA (*Am. J. Roent. and Rad., Therap.*, 1930, 24, 673) conclude that Roentgen therapy is of considerable aid as an auxiliary to surgical procedures in the treatment of operable mammary carcinoma. In the cases without glandular involvement the addition of irradiation does not seem to increase noticeably the five-year results above those of surgery alone, assuming that all diseased tissue is removed. But in the carcinomas that have spread to the axillary or high thoracic lymph nodes, the five-year results are almost doubled. The best method of procedure is a combina-

tion of radical surgery with a thorough systematic irradiation of the entire anterior thorax, axilla and neck on the diseased side. In the inoperable or recurrent carcinomas, Roentgen therapy produces prolongation of life if the lesion is localized to the adjacent lymph nodes or anterior thorax, and alleviates the symptoms if the carcinoma is already generalized.

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**The Effect of Roentgen Rays on the Thyroid and Parathyroid Glands.**—From their experimental studies WALTERS, ANSON and IVY (*Radiol.*, 1931, 16, 52) conclude that the histology of the normal thyroid of the dog is not materially altered by a Roentgen ray dosage known to be of value in certain cases of hyperthyroidism. The tendency of the effect was in the direction of hyperplasia. The treatment caused a definite hyperplasia of the parathyroids. A gradual slight decrease in blood calcium occurred in spite of the parathyroid hyperplasia. It is pointed out that these results do not necessarily apply to the hyperplastic thyroid of Graves' disease.

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**Deep Roentgen Ray Treatment of Chronic Gonorrheal Infection in the Female.**—Six cases of gonorrheal infection of the vagina, urethra and cervix were subjected to deep Roentgen ray therapy by HENRY (*Radiol.*, 1931, 16, 47). The results in all cases were practically the same. The erosions disappeared from the cervix, the discharge became very thin, and the general health improved. Smears taken over a period of four months after treatment failed to reveal the presence of gonococci in 5 of the 6 patients. One patient menstruated three weeks after treatment; 2 after six months; 1 after seven months; and 2 after one year. One patient became pregnant three months after treatment. The infections in the 6 cases had existed for two to nine years.

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**Roentgenologic Appearance of Interlobar and Mediastinal Encapsulated Effusion in the Thorax.**—FREEDMAN (*Radiol.*, 1931, 16, 41) states that interlobar effusions are characterized roentgenologically by sharply defined band or wedge-shaped or circular shadows in the region of the interlobar septa. They require to be distinguished from lobar and marginal pneumonia, caseous consolidations and bronchial carcinomas. Mediastinal pleural effusions are represented by band-, wedge-shaped or triangular shadows parallel to the vertebral column or to the cardiac silhouette. They are imitated more or less by pericardial effusions, paravertebral abscesses, aortic aneurysms mediastinal tumors and areas of bronchiectatic consolidation.

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**Blood Changes in the Leukemias and the Lymphomata and Their Bearing on Roentgen Therapy.**—Roentgen irradiation, according to ISAACS (*Am. J. Roent. and Rad. Therap.*, 1930, 24, 648) stimulates primitive myeloblasts and lymphoblasts to rapid reproduction. Myelocytes and small lymphocytes are stimulated to finish their life history and they then die or are excreted. The matured cells are excreted into the gastrointestinal tract—polymorphonuclear cells into the mouth, lymphocytes into the intestines. Very rapid excretion may result in a decrease of the number of cells in the peripheral circulation (leukopenia) giving the false impression of an aplastic bone marrow.

## NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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**A Brief Résumé of the Types of Insanity Commonly Met With in India, With a Full Description of "Indian Hemp Insanity" Peculiar to the Country.**—EDULJI DHUNJIBHOY and BOMB (*J. Ment. Sci.*, 1930, 76, 254) lists the types of insanity in the order of their frequency as met with in a mental hospital in India. The order as given is: Manic-depressive psychosis; dementia præcox; toxic psychoses (a) hemp, (b) alcohol, (c) secondary to starvation and physical exhaustion, (d) infection, pregnancy and the puerperium; mental defectives; epilepsy; paraphrenia and paranoia; primary and secondary dementia; senile, traumatic and arteriopathic psychoses; encephalitis lethargica; general paralysis; psychoneuroses. The author comments upon the rarity of general paresis and states that he has never seen a case in an Indian who had never been abroad, but has seen 2 cases in those who had traveled. The description of "Indian Hemp Insanity" follows. He describes two types—acute mania and chronic mania, together with a secondary dementia. The primary symptomatology in acute mania is an intense excitement accompanied by visual and auditory hallucinations usually referring to beautiful women who talk and copulate with the patient. The attack is of shorter duration and relapses are infrequent if the drug is stopped at once and recovery is the rule. Complete amnesia for all events is found on recovery. There is a characteristic dare-devil demeanor with an irresistible impulse to wilful damage. There is a history of the drug habit, and absence of a psychopathic or neuropathic history. In addition, a peculiar eye condition is seen in which there is a conjunctival congestion of the horizontal vessels of both eyes. In the chronic mania the symptoms are less severe but there is a general expansivity. Complete loss of speech, lasting for a prolonged period after recovery, is sometimes seen, and one case is cited in which speech was lost for eight years. In the more chronic forms the acute congestion of the eye vessels is replaced by a well-marked line of blood pigments in the same situation. The prognosis is very hopeful. In the acute cases 90 per cent recover while in the chronic cases about 40 per cent recover. Postmortem examination revealed no gross abnormalities. Treatment is complete removal of the drug as no withdrawal symptoms are manifested.

**Hypophrenia as a Symptom of Juvenile Paresis.**—POTTER (*The Psychiat. Quarterly*, 1931, 5, 1) presents 11 cases of juvenile paresis wherein he demonstrates the importance of syphilis as one of the etiologic factors in psychiatric problems in children—especially among the mentally defective class. He states that there is a generally pre-

valent opinion among physicians in charge of institutions for care and treatment of the mental defective that syphilis has little, if any, causal relation in mental deficiency. The reason for this opinion, he explains, is that there has been too much dependence placed upon statistics and not enough attention given to detailed clinical examination and interpretation of facts. The cases in his series are presented briefly from a clinical point of view and leave no doubt concerning their diagnosis. Each exhibits the presence of parental syphilis, the presence of the characteristics of retardation, a low intelligence quotient, positive physical findings and significant serological studies. From this material he draws the conclusions that: (a) direct infection of the central nervous system (neurosyphilis) in cases of congenital syphilis occurs with such sufficient frequency that it is not to be regarded as a rare or uncommon phenomena; (b) congenital cerebral syphilis always results in mental pathology; (c) the mental pathology of cerebral syphilis may be expressed by various gradations of hypophrenia usually accompanied by emotional instability without any outstanding psychotic manifestations; (d) the organic neurologic symptoms of congenital neurosyphilis may be expressed by either a well-defined hemiplegia on the one hand or merely exaggerated patellar reflexes and sluggish pupils on the other; (e) the serologic findings in the blood and spinal fluid depend on the relative activity of the syphilitic process—that in some cases both the blood and spinal fluid Wassermann is strongly positive with lymphocytosis, albumin and a paretic or luetic type of gold chlorid curve in the spinal fluid, while the other extreme may be found in other cases in which the only positive serology is manifested by a weakly positive paretic or luetic gold chlorid curve in the spinal fluid; (f) a history of parental syphilis is always present and the characteristic history of miscarriages, still births and other evidence of congenital syphilis is commonly obtained with reference to the siblings of the patient; (g) when the central nervous system is invaded by the syphilitic infection in early childhood, infancy or even *in utero*, the mental symptomatology is confined almost exclusively to the field of intelligence even when the involvement is of a parenchymatous type.

## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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**The Pituitary Factor in Arteriosclerosis. Its Experimental Production in Rabbits.**—Several workers had previously produced arteriosclerosis in rabbits, by feeding diets high in fat or lipid substances. It had also been noticed that a marked hyperplasia of the suprarenal

cortex with a lipoid storage took place in arteriosclerosis, hypertension and nephritis. Thus the importance of suprarenal cortex and cholesterol metabolism was suggested. MOEHLING and OSRUS (*Ann. Int. Med.*, 1930, 4, 578) knowing the close relationship between the pituitary gland and fat and carbohydrate metabolism, suggested that the pituitary secretion was a factor in arteriosclerosis. The authors desired to show the correlation between the pituitary and suprarenal glands in the production of arteriosclerosis. A series of four groups of healthy rabbits were used. The first group was used as a control, and fed on a normal laboratory diet. The second group was fed on a high cholesterol diet. The third group was fed on the same high cholesterol diet plus the addition of a daily injection of 1 cc. of pituitrin (posterior lobe extract). The fourth group was fed on a normal laboratory diet plus the addition of daily injection of 1 cc. of pituitrin. The animals were kept on such a routine for one hundred days and then autopsied. The authors were able to demonstrate that with the injection of posterior lobe extract alone, even without the influence of diet that a marked suprarenal cortex hypertrophy took place which they believe is an important link in the production of arteriosclerosis. The authors also showed that marked atheromatous plaques could be produced in the rabbit's aorta, within a period of one hundred days by feeding a diet high in cholesterol along with a daily injection of posterior lobe pituitary extract.

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**Etiology of Disseminated Sclerosis.**—Ever since Charcot described disseminated sclerosis as a distinct morbid entity, numerous attempts have been made to discover a specific etiologic agent. Spirochetes were at one time considered as possibly responsible but the evidence failed to support this view. Focal infections in tonsils (Woodbury, 1919) and about the teeth (Dor, 1924) have been thought to be responsible but this factor has not been accepted as of prime importance. A specific neurotropic virus has been advanced by many as possibly the type of agent active in this disease. The recent report of CHEVASSUT (*Lancet*, 1930, i, 552) aroused considerable interest because of her claim that she had not only discovered the specific virus but had succeeded in obtaining cultures of it. She described the morphology and biologic characteristics of the "virus" and vaccines were prepared which PURVES-STEWART (*Lancet*, 1930, i, 560) used as a specific treatment in his patients with disseminated sclerosis. In temporary conjunction with HICKS and HOCKING (*Lancet*, 1930, i, 612) certain studies were made of pathologic and biochemical changes produced by this "virus" which did not lead to any definite or very helpful conclusions. (The Abstractor had the opportunity to visit the laboratories of Westminster Hospital where this work had been carried out and after investigating the subject for about four weeks and consulting with many of the leading medical research workers in London his conclusions were: there is no proof that the causative agent has been discovered; the controls used were inadequate; many attempts to confirm Chevassut's results have failed and the evidence of a curative value of the vaccines is quite incomplete. The characteristic tendency of disseminated sclerosis to undergo spontaneous remissions, sometimes of very long duration,

makes it particularly difficult to evaluate any method of treatment. In this particular method involving as it does the intravenous or intrathecal administration of a "specific vaccine" which from the nature of the materials used cannot exclude the element of shock, will demand the most rigid statistical study because on the clinical results obtained rests the burden of proof that a virus has been discovered. This is true even if the various phases of the study of "cultures" could be repeated by others, or clean-cut evidence were available that the phenomena described are to be obtained exclusively with the cerebrospinal fluid from patients with disseminated sclerosis.) At a meeting of the Royal Society of Medicine CARMICHAEL (*Brit. Med. J.*, 1931, i, 97) opened a discussion on the above subject, which at least indicated that much more must be done before the work of Chevassut and her associates can be accepted as reliable evidence that the agent of disseminated sclerosis has been discovered.

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**Studies of Skin Reactions in Hypersensitiveness.**—In attempting to differentiate between the types of anaphylactic and tuberculin reactions DIENES (*Proc. Soc. Exper. Biol. and Med.*, 1930, 28, 72) has studied the histologic changes especially during the first hours after the injection of antigen and found marked differences. The anaphylactic type of reaction with a quickly developing and transient wheal is followed, after the development of edema and the vascular changes, by a more or less intense accumulation of leukocytes which is sometimes well-developed one to two hours after the injection. An accumulation of mononuclear cells (more intense in tuberculous animals) comes after the macroscopic reaction has subsided. The tuberculin reaction is different. If it is slight there occurs a strong accumulation of mononuclear cells around the bloodvessels, often before any macroscopic sign of the reaction. After twenty-four hours, even in very slight reactions, the whole reacting area is markedly infiltrated with mononuclear cells and more or less polymorphonuclear leukocytes in the center, depending upon whether the reaction is strong or weak, but always associated with the mononuclear cell infiltration. Even in reactions with central necrosis the early stages are as described and the leukocytic reaction follows tissue injury. Tuberculous guinea-pigs sometimes give this type of reaction even after normal saline. It is in the order and degree of these cellular reactions that the differences in the two types of reactions are to be found. In a second report (Same, p. 75) the author studied the sequence of events in tuberculous guinea-pigs in which egg white was introduced into the tuberculous lesions. He found the immunization process was more rapid and often there developed a strong tuberculin type of skin sensitiveness to egg white never seen in normal animals. This stage is followed by the other manifestations of sensitiveness, viz.: acute anaphylaxis, anaphylactic type of skin reaction, the protracted anaphylactic shock and the appearance of antibodies in the serum. These results suggested that in normal animals a phase corresponding to the tuberculin sensitiveness might occur and may have been overlooked. In support of this he found five to seven days after treatment that the slight skin reactions were suggestive of very slight tuberculin reactions in that they often are delayed

and persist for forty-eight hours. Carefully timed preparations of these reacting areas gave the evidence of a mononuclear cell response at the site of injection and a relatively slight influence on the circulation. The author concludes that the tuberculin type of skin sensitiveness is probably an exaggerated development of this first phase of the immunization process and is therefore of great interest in the study of immunity in infectious diseases.

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## HYGIENE AND PUBLIC HEALTH

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UNDER THE CHARGE OF

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**Psittacosis: Epidemiologic Considerations With Reference to the 1929-1930 Outbreak in the United States.**—ARMSTRONG (*Public Health Reports*, 1930, 45, 2013) notes briefly the earlier occurrence of psittacosis in the United States and gives the outstanding features of the 1929-1930 epidemic in considerable detail. There were recorded 74 foci of infection with a total of 169 cases, with 33 fatalities; these were distributed among 15 states and the District of Columbia, but they do not include laboratory infections. It is insisted that psittacosis is a clinical entity, and one not readily confused with ordinary pneumonia, and that birds are etiologically related to its occurrence in man. Parrots occasioned by far the larger number of cases, with parakeets, "love birds," and canaries contributing a few cases each. It is stated that many thousands of birds are imported annually and that they come from many tropical and subtropical countries. The infectiousness of the disease from birds to man is very high but from man to man almost *nil*. The incubation period is ordinarily ten days, but varies from six to fifteen days. The disease is more prevalent among women than among men, doubtless due to better opportunities for contact. The clinical symptoms are described as follows:

The disease may begin suddenly with chilly sensations, fever and headache, or these may appear after a few days during which the patient has not felt exactly well. The fever when first recorded is usually 100° to 102° F. and tends with irregular remissions to rise to a height of 103° to 105° during the second week. The pulse is likely to be slow, considering the temperature. Nosebleed is not uncommon. Focal lung lesions with physical signs may be present at the first examination or appear after three or four days. There is usually but little cough or expectoration early, but these may develop later.



The cough is usually nonproductive. Chest pains may be present. The tongue, as a rule, presents a heavy white to brownish coat, with red edges, but may be cracked and dry. The appetite is lost and constipation is the rule. Abdominal distention is troublesome in many cases. Albuminuria is a very constant accompaniment after the disease is established, and retention may be present. "Rose spots" have been occasionally reported.

The blood count is usually normal or slightly above normal during the first few days, but a leukopenia is the rule later on. In one case the count was as low as 600 cells on the twentieth day of illness, but counts from 3000 to 5000 are more common. Delirium is common when the temperature is high; stupor may be present. Dreams are likely to disturb the sleep, and insomnia may be troublesome. The fever may terminate after about eight days or continue for three weeks or more. The following table shows the relative frequency of occurrence of the more common symptoms as reported for the 169 cases:

MOST FREQUENTLY RECORDED SYMPTOMS IN 169 CASES.

Symptom.	Number of cases in which present.	Number of cases in which absent.	Unknown.
Headache . . . . .	112	13	44
Malaise . . . . .	107	14	48
Cough . . . . .	106	23	40
Chills . . . . .	98	25	46
Pains other than head . . . . .	95	28	46
Anorexia . . . . .	92	24	53
Constipation . . . . .	87	36	46
Coated tongue . . . . .	85	20	64
Delirium or stupor . . . . .	48	69	52
Nosebleed . . . . .	25	96	48
Diarrhea . . . . .	13	110	46

*Relapses.* Relapses are not uncommon. Three of the 11 Hygienic Laboratory cases suffered relapses during the first three weeks following the return of the temperature to normal. The relapses began with symptoms similar to the original onset but ran milder courses, the temperature rising to 100° to 102° F. and then gradually falling in a few days. A relapse occurred in another case in Washington after three weeks of normal temperature. These four relapses occurred among some 13 cases treated with convalescent serum, and one wonders if this form of treatment predisposes to relapse.

*Complications.* Phlebitis is the most common complication. The death rate is about 24 per cent in persons over thirty, but no death occurred below that age.

**Antirabic Vaccine Paralysis.**—McCoy (*Pub. Health Rep.*, 1930, 45, 1888) gives the following as the chief theories as to the cause of this condition: (a) That it is due to anaphylaxis resulting from the injection of foreign animal tissue (rabbit's cord); (b) that it is due to a "toxin" elaborated by the specific organism of rabies; (c) that it is due to rabies resulting from street virus received at the time the bite was inflicted; (d) that it is due to rabies resulting from fixed-

virus infection; (e) that it is due to infection with extraneous organisms introduced with the virus during treatment; (f) that it is due to hysteria and other neuropsychologic disorders. Perhaps at the present time one would like to add the suggestion that the anti-rabic vaccines may activate a virus lying dormant in the body or may serve to enhance susceptibility to an ordinarily nonpathogenic virus. Another thought that will occur to one familiar with the frequency of pathologic processes in the central nervous system of rabbits is the possibility of the occasional susceptibility of man for a virus normally, or perhaps we had better say, commonly, found in rabbits. There were 8 cases of paralysis among about 25,000 treatments, but no evidence to incriminate any special form of treatment.

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**A Study of Ventilation and Respiratory Illness in Syracuse Schools: With an Analysis of Factors Affecting Criteria Used.**—The New York State Commission on Ventilation, in its 1923 report, presented data which suggested that the system of fan ventilation commonly installed in American schools is not only unnecessary but undesirable. The work of the Commission appeared to indicate that respiratory disease among pupils is actually more prevalent in fan-ventilated schools than in schools provided with a simpler and more economic system of window supply and gravity exhaust. So far as the main issue is concerned, observations of a similar trend have been made by three independent observers: Greenburg, at New Haven, Conn., Childs, at Cleveland, Ohio, and Shaughnessy, at Chicago. Recently the Commission has devoted itself to the study of certain other types of ventilation and of certain modifications of fan ventilation (*Am. J. Hyg.*, 1930, 12, 196). Conditions have been observed in three furnace-gravity schools, one fan-gravity school and two fan-fan schools for 3 years, and in one other fan-gravity school, two other fan-fan schools and two window-fan schools for 2 years and in two other fan-gravity schools for 1 year. In this study of Syracuse schools a group of old-fashioned schools ventilated by furnace inlets and gravity exhaust ducts shows in each of 3 years lower absence rates due to respiratory disease than did groups of more modern schools ventilated by either plenum or exhaust fans. On analysis, it appears that the observed differences were due in part to the fact that the furnace-gravity schools were situated in districts largely inhabited by a foreign-born population. If, however, allowance be made for this factor, these schools still show an apparently lower respiratory disease absence rate than that of the mechanically ventilated schools. However, the authors are not disposed to stress the better record of these schools. It is evident that the comparison of different schools is open to serious errors and one can rarely be certain that all such errors have been eliminated.

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**Rate of Air Flow and Room Temperature in Relation to the Health of School Children.**—The results of this study by the New York Commission (*Am. J. Hyg.*, 1930, 12, 215) are largely negative ones; but it is believed that they are of value as a contribution to the technique involved in such investigations. They appear to indicate that respiratory illness absenteeism and even data in regard to respiratory illness

according to Burn and Marks, normal rabbits show an increase in response to insulin after thyroidectomy of 6 and possibly 9 times, and so far as our experiments have progressed Burn and Marks' figures have not been exceeded in the normal rabbit. The thyroid, therefore, seems to be one factor in this phenomenon of spontaneous insulin resistance, and these results tend to support the view that the thyroid influences the sensitiveness of the response of the sympathetic nervous system.

However, these resistant rabbits after thyroidectomy still did not respond to the very small doses of insulin to which a normal rabbit responds after thyroidectomy, so that there must be other factors than the thyroid concerned in this insulin resistance.

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**Carotid Sinus Reflexes and Respiration.**—CARL F. SCHMIDT (from the Laboratory of Pharmacology, University of Pennsylvania). Perfusion of the carotid sinuses of 15 dogs with Ringer's fluid, or with blood taken from and returned to a donor dog, has regularly shown respiratory depression or apnea on raising sinus pressure, stimulation sometimes very marked, on lowering it, the effect intensified by section of the vagodepressor nerves, entirely abolished by denervation of the sinuses. Similar results were obtained in 2 cats, but in a rabbit there were no respiratory effects, though circulation was very markedly influenced. This confirms Heymans' observations (*J. Physiol.*, 1930, 79, 254; *Arch. internat. de pharm. et de therap.*, 1930, 39, 400), that reflexes from the carotid sinuses can affect respiration profoundly. Heymans' conclusion, that respiratory responses to changes in blood pressure are wholly due to carotid sinus and aortic reflexes, has been shown to be too sweeping by four sorts of experiments: (1) Adrenalin causes apnea in dogs, cats and rabbits whose vagodepressor or depressor nerves are cut and whose carotid sinuses are completely denervated, and acetyl cholin and nitroglycerin cause marked respiratory stimulation in the same animals; in perfusion experiments (dogs) adrenalin injected intravenously is more depressant to respiration when carotid sinus pressure is low than when it is high. (2) Apnea is produced in the dog and cat when occluded vertebral and carotid arteries are released, and the effect is exactly the same whether the occlusion is made proximal to the carotid sinuses (common carotids) or distal to them (external and internal carotids), or whether the sinus nerves are intact or cut; CO<sub>2</sub> inhalation reduces somewhat the apnea consequent upon release of the vessels after carotid sinus denervation, but the apnea is by no means prevented thereby, showing that it is not due to loss of CO<sub>2</sub> during the occlusion. (3) Abrupt increase in intracranial (cisterna magna) pressure in the dog to a level equal to or exceeding arterial blood pressure causes hyperpnea and apnea occurs when intracranial pressure is abruptly lowered; smaller rises in intracranial pressure, to half arterial pressure or even less, cause definite respiratory stimulation. (4) When the brain of the rabbit is perfused by way of the internal carotids with the animal's own blood, by means of a pump, respiration is markedly stimulated by reduction and markedly depressed by increase in pump output, though the carotid sinus nerves are excised and the depressor nerves are cut. There may be other reflexes from

cerebral vessels or meninges, but these effects are certainly not dependent wholly upon aortic depressor or carotid sinus reflexes (Heymans); apnea is produced by release of occluded carotid and vertebral arteries in decerebrated dogs and cats after sinus denervation, so that the reflexes, if they exist, must arise in the brain stem. Change in blood supply of the center seems the more probable explanation.

Heymans (*Arch. int. de pharm. et de therap.*, 1930, 39, 400) found the respiratory effects of changes in blood-gas tension to depend largely upon carotid sinus reflexes in dogs. In 5 crossed-circulation experiments on dogs no evidence of such dependence could be obtained, though sensitivity to pressure changes was established in all. Heymans' positive results could be duplicated in dogs only if blood from the donor was allowed to enter the cerebral circulation of the recipient (3 experiments) and occlusion of the vascular communication abolished the "reflex" effect. In two similar experiments on cats, however, there were marked reflex effects like those described by Heymans in dogs.

It seems necessary to conclude that in the respiratory effects of changes in blood pressure both reflex and central blood flow influences are concerned, and the problem becomes one of quantitative evaluation of the two. Carotid sinus reflexes to respiration are aroused (in crossed-circulation experiments) by changes in pressure amounting to about 10 per cent; when the pressure change is maintained respiration gradually escapes from the reflex influence, and the response depends upon change in pressure rather than upon any given pressure level. Attempts at evaluating the blood flow factor have been made upon 7 dogs, measuring cerebral venous outflow from the torcular herophili; the results so far have been obscured by unaccountable spontaneous changes in cerebral venous pressure and outflow. Evidence now at hand suggests that the aortic depressor and carotid sinus nerves may be extrinsic afferents to a cerebral vasomotor nervous mechanism, and that their function is to antagonize the tone of bloodvessels supplying vegetative areas of the brain, the effective stimulus being pressure in aorta and carotid sinus. This possibility is under investigation.

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**Observations on Living Lymphatic Capillaries in the Rabbit.**—E. R. and E. L. Clark (illustrated in part by motion pictures taken by E. A. SWENSON and E. R. CLARK) (from the Department of Anatomy, University of Pennsylvania). In the new tissue which invades the space left in the modified type of transparent chamber introduced into the rabbit's ear (*Anat. Rec.*, 1930, vol. 47) new lymphatic capillaries have been observed and their mode of growth, morphologic characteristics and some of their physiologic properties have been studied microscopically with daily photographic and camera lucida records over periods of weeks and months. So far as known this is the first time in which it has been possible to observe the finer microscopic details of lymphatic capillaries in the living mammal.

Studies to date have revealed the following facts:

1. Lymphatic vessels grow by endothelial sprouting. Pushing out of protoplasmic tips from preëxisting lymphatic endothelium has been observed repeatedly with the oil-immersion lens. Mitotic division of the endothelial nuclei of the tissues of lymphatic capillaries has been

observed and the times of the different phases recorded. Following the division the daughter nuclei always remained attached to the vessel wall.

2. The invasion of a new area by lymphatic capillaries is subsequent to that of fibroblasts and new bloodvessels by days or weeks. In cases in which they followed closely behind bloodvessels they were found to grow between the vessels and to form a loosely anastomosing plexus completely independent of the bloodvessel network. In cases where their invasion of the observation area was delayed the lymphatics grew in a loose space just adjacent to arteriole or venule. In either case the number of new lymphatic sprouts was much less than that of the new blood capillaries.

3. Lymphatic capillaries are normally closed at the tip. However, following injury openings have been produced in the walls of certain vessels which persisted for as long as a week; through these the passage back and forth of hundreds of erythrocytes to and from the space beyond the growing zone of vessels was observed. In every case such artificial openings eventually closed.

4. Movement of lymph in the newly formed lymphatic vessels is very sluggish—frequently the same leukocytes or erythrocytes remained in a capillary for several days. Erythrocytes and polymorphonuclear leukocytes showed degenerative changes inside the lumen of the lymphatic capillaries within two to five days.

5. In inflammatory conditions the lymphatics were observed to show dilatation accompanied by stasis.

The back-and-forth movements of blood cells inside the lymphatic capillaries, together with circulatory changes in neighboring bloodvessels were shown in motion pictures.

In addition, motion pictures were shown of active contractions of arteriovenous anastomoses present in two of the transparent chambers in which the early formation of bloodvessels and their subsequent changes had been followed over a period of 10 months.

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ORIGINAL ARTICLES.

PRESENT STATUS OF THE CLASSIFICATION, PATHOLOGY  
AND ETIOLOGY OF CHRONIC RHEUMATIC DISEASE.

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ONE of the outstanding problems in chronic arthritis is uniformity of classification. Much of the literature on this subject is unintelligible on account of the failure to specify the particular type of disease under discussion. Very frequently no attempt is made to differentiate the two types. Even when such a distinction is made, the terms may be confusing.

**Classification.**—Both from a pathologic and clinical standpoint, two fairly easily distinguishable types can be recognized. These two types are probably etiologically different and not unlikely require different therapy. At the recent congress at Liège it was decided that at least for statistical purposes a uniform nomenclature should be adopted for English, German and French writers. In English the two terms recommended were rheumatoid arthritis (infective peri-arthritis) and osteoarthritis. Some of the terms which in the past have been used synonymously with rheumatoid arthritis are: atrophic arthritis, chronic infective arthritis and arthritis deformans. Hypertrophic arthritis is synonymous with osteoarthritis. The pathologic studies of Nichols and Richardson<sup>1</sup> led them to use the pathologic descriptive term, "proliferative arthritis," corresponding to the clinical rheumatoid arthritis, and "degenerative arthritis," corresponding to the clinical osteoarthritis. Their studies gave us for the first time a clear pathologic picture of the two types.

The not infrequent presence of mixed forms, that is, rheumatoid arthritis and osteoarthritis, in the same patient has given rise to considerable confusion. In this presentation an attempt will be made to clarify this point. If we include mixed forms in our classification at least 95 per cent of cases can be properly assigned.

**Pathology of Rheumatoid Arthritis.**—The outstanding contribution to the literature on joint pathology in chronic arthritis is the work of Nichols and Richardson. Recently their findings have largely been confirmed, with some additions, by Fisher.<sup>2</sup> From the standpoint of etiology they both emphasize the importance of studying the changes that occur very early in the disease, as the later changes may be due, in part, to trauma or unequal pressure on the joint cartilages following the initial lesion. The following description of pathologic changes is derived largely from these two sources.

In the earliest stage there is a round-cell proliferation, beginning at the junction of the synovium with the articular cartilage. This cellular proliferation slowly spreads over the articular surface until the entire cartilage is covered by a highly vascular membrane resembling granulation tissue. This pannus invades the superficial layers of cartilage which it destroys. This granulative tissue is later replaced by connective and finally by fibrous tissue. The articular surface eventually is covered with a dense fibrous tissue. The synovial round-cell infiltration is not confined to the articular surfaces, but extends into the periarticular tissues, thus accounting for the spindle-shaped deformity. Fibrosis develops later and may become a contributing factor in ankylosis.

Simultaneous with the synovial changes there is a marked round-cell infiltration and proliferation of the villi. The villous outgrowth may extend to the center of the joint. The vessels in these villi later undergo an obliterative endarteritis, leading to necrosis and fibrosis.

While the above inflammatory reactions are taking place, and sometimes subsequent to them, changes can be observed in the subarticular cancellous spaces. Connective-tissue cells appear in the narrow spaces associated with the development of new blood-vessels and eventually bone absorption, resulting in enlarged cancellous spaces. Later, the subarticular bone shows an increased density. The deep layers of the joint cartilage, adjacent to the head of the bone, are attached from below, undergoing changes similar to those described in the superficial layers. The fibrous covering of the articular surface, therefore, is made up of two superimposed layers—one arising from the hyperplasia of synovium; the other from the subarticular bone.

The above-described lesion does not usually involve all the cartilaginous surface equally; rather there is a tendency to a patchy disintegration. In some areas there may even be an attempt at proliferation of cartilage. In other areas the cartilage may be

destroyed before new fibrous tissue is found, and the bone thus exposed may lead to a bony ankylosis with the adjacent bone on the opposing joint surface. Fibrous ankylosis, however, is much more frequent. In case fibrous ankylosis has taken place, new cartilage and bone may be formed in the fibrous tissue, leading to the second type of ankylosis. By regular movement of the joint throughout the disease, fibrosis and bony ankylosis may be prevented.

There is a secondary bone atrophy, as shown by the Roentgen rays, which at least in part is due to disuse and is most marked in those cases with ankylosis.

The character of the joint changes speaks strongly for an infective origin. This view receives further support by the finding of microorganisms, in a limited number of patients, in the blood, joint fluid and adjacent lymph glands. Fisher<sup>2</sup> claims that there is no essential difference in the gross or microscopic pathology of the joint in rheumatoid and gonorrheal arthritis.

**Pathology of Osteoarthritis.**—The changes in the joint, as described by Nichols and Richardson and Fisher, are degenerative, not inflammatory. The earliest lesion found is fibrillation of the cartilage. Normal cartilage on bending shows striæ. Fibrous tissue develops in these striæ, resulting in ridging of the cartilage followed by vertical cracking. These changes are most marked toward the center of the joint. This is possibly due to poor vascularity. Following the cracking, the cartilage degenerates, often giving an irregular pitted appearance. The bottom of the pit may show exposed bone. In addition, the joint surface may show rounded elevations due to proliferation of cartilage, and these areas may later ossify. The new bone formation usually begins long before the cartilage is destroyed.

The peripheral cartilage may remain normal for years after the central portion has degenerated. Sooner or later, however, the marginal cartilage undergoes a hyperplasia, resulting in lipping. Fisher looks upon this as a compensatory reaction to increase the articular surface. Later, this marginal lip undergoes ossification, giving rise to the osteophytes which characterize this type of arthritis. The bone beneath the cartilage increases in density even before the degeneration of the cartilage.

In contradistinction to the rheumatoid type, changes in the synovium develops only after lipping has appeared and is limited to a proliferation of the villi. Existing villi hypertrophy and new villi are formed. Chondromata may develop in the villi and later become detached, and in this manner loose bodies are formed. Their presence may account for the recurrent synovitis so frequently observed in patients with osteoarthritis. The villous proliferations differ from those observed in rheumatoid arthritis, not only in their later appearance, but also in the form of the villi—they are much shorter, do not extend over the entire joint surface and do not show



the same tendency to degeneration. The crunching sound elicited in the knees in osteoarthritis is due to rubbing together of these villous masses.

Bony or fibrous ankylosis in osteoarthritis is practically unknown; interference with motion arises from interlocking of the osteophytes. Muscle atrophy when present is rarely marked, and consequently the deformities observed in rheumatoid arthritis are lacking.

From a pathologic viewpoint it is apparent that chronic arthritis may be divided into two distinct types. Such difference in pathology strongly suggests a difference in etiology.

**Etiology of Rheumatoid Arthritis.**—There is abundant clinical evidence that rheumatoid arthritis is infective in character. It appears with the most acute onset in children and is frequently referred to as Still's disease. Fever, leukocytosis, inflammation of the joints, enlarged spleen and lymphatic glands is abundant evidence of its infective nature. The disease in adults is usually more insidious in its onset. It appears most frequently in a phalangeal articulation, and there may be only moderate evidence of infection. In the early stages there is always some evidence of inflammation. The course of the disease is usually one of remissions and exacerbations, with a tendency for the evidence of infection to disappear, leaving, however, the characteristic spindle-shaped deformity. In such a joint there may not be any evidence of infection. Not knowing the previous history, one might be led to conclude that the disease was not infectious. This, I believe, explains the position of some orthopedists, that this represents a distinct type to which they apply the term atrophic arthritis. In some cases, not necessarily of long standing, the active disease may entirely disappear, and not infrequently permanently, leaving, however, a crippled patient with atrophied and distorted extremities.

The result of blood, lymph gland and joint cultures during the stage of activity lends support to the infective view. Rosenow<sup>3</sup> cultured the regional lymph glands in 54 patients. In 32 he recovered nonhemolytic streptococci. Billings, Coleman and Hibbs,<sup>4</sup> made cultures of regional lymph nodes in 28 patients. Of these 19 showed nonhemolytic streptococci, 1 showed a hemolytic streptococci and 1 a mixture of the two forms. They made joint cultures in 19 patients, 5 of whom showed nonhemolytic streptococci and 1 a mixture of hemolytic and nonhemolytic streptococci.

Richards<sup>5</sup> made blood cultures from 104 patients with "chronic arthritis" and recovered *Streptococcus viridans* in 18.

Cecil, Nicholls and Stainsby,<sup>6</sup> with care in the selection of cases, obtained positive streptococcus cultures from the blood in 61.5 per cent of patients. Of these streptococci 83.3 per cent he considered attenuated hemolytic streptococci, the remainder being viridans or indifferent strains.

Forkner, Shands and Posten<sup>7</sup> secured positive joint cultures in

22 per cent of their cases. Positive cultures from the neighboring lymph nodes were obtained in 47 per cent. The microörganism in both joint and gland was a nonhemolytic streptococcus.

Cecil, Nicholls and Stainsby<sup>8</sup> have obtained cultures of streptococci from the joints in 33 out of 49 patients or in 67.3 per cent. Cultures obtained from both blood and joints were agglutinated in a very high titer by the patient's blood.

Other investigators, however, have found staphylococci and diphtheroids rather than streptococci. The predominance of streptococci in cultures speaks strongly for this being the most frequent causal agent. However, it speaks against a specific streptococcus as the etiologic agent. Whether rheumatoid arthritis is due to a specific streptococcus, or whether different microörganisms are capable of producing these changes, is still an open question.

Dawson, Olmstead and Boots<sup>9</sup> made agglutination tests with various strains of streptococci, using serum from patients with rheumatoid arthritis. They found that the serum agglutinated all strains of hemolytic streptococci in a very high titer. The agglutinating was just as marked with cultures from erysipelas, scarlet fever or rheumatic sore throat as with the special *Streptococcus hemolyticus* isolated by Cecil from rheumatoid arthritis.

No attempt will be made to discuss the possible allergic character of rheumatoid arthritis. If it can be demonstrated that a synovial proliferation may be a type of allergic reaction, then allergy must be considered as a possible etiologic factor.

The focus from which the bacteria reach the blood stream and finally the articular surface is so highly speculative that discussion is futile. Some emphasize especially the digestive tract or urinary tract, others the teeth and tonsils and, finally, there are those who believe that acute nasopharyngeal or tracheal infections (rather than chronic foci) are responsible for the joint involvement.

Patients with rheumatoid arthritis show marked evidence of vascular disturbance in the involved extremity. Pale and cold skin is apparently a constant accompaniment of this disease. The beneficial results of ganglionectomy described by Rowntree and Adson<sup>10</sup> suggest that ischemia may be an important factor in preventing recovery. They claim that in the more acute types of rheumatoid arthritis evidence of inflammation readily subsides after the operation. Rowntree believes that ischemia may be an important etiologic factor. This is in accord with Llewellyn's<sup>11</sup> observations, that evidence of inadequate blood supply precedes the joint involvement.

**Etiology of Osteoarthritis.**—The pathology of the joints, at least of the extremities, that has been studied and the clinical signs and symptoms indicate a noninfective etiology. Many theories have been advanced as to the etiologic agencies that might explain degeneration of cartilage, which is the outstanding pathologic finding.

Fisher claims "osteoarthritis is not a disease *sui generis*, but a physiological response to some form of irritation either mechanical or chemical." He arrived at this conclusion after a careful study of the normal and pathologic physiology of the knee joint. He did some experimental work on rabbits by shaving off a thin layer of cartilage from the center to the periphery of the articular cartilage. Six weeks later the animals were killed. The central portion of this cartilage showed no tendency to regenerate; in fact, it was necrotic. The peripheral portion, however, showed marked regeneration. He concludes that trauma, which will cause degeneration of the central cartilage, is followed by proliferation of the marginal cartilage. This difference in reaction he ascribes to the better vascularity of the peripheral portion. It is his opinion that damage or loss of the central cartilage gives rise to a sequence of events physiologic and compensatory in character which we recognize as osteoarthritis.

Key<sup>12</sup> has discussed the relation of traumatic or mechanical factors to experimental osteoarthritis. In addition to his own experimental work, he reviews the literature on this phase of the subject. The earliest experiments were performed by Axhausen, who destroyed a portion of the knee cartilage in rabbits with iodine or ammonium hydroxid. When the animal was killed after a lapse of several weeks the pathologic changes in the joint resembled those found in osteoarthritis in man. Others have obtained similar results by impairing the blood supply to a portion of the cartilage or by traumatizing the joint. Key has produced osteoarthritis in rabbits by resecting a small piece of cartilage from the patella and at the same time causing unequal pressure or strain by giving the rabbit a knock knee. Pemberton<sup>13</sup> refers to work done by one of his associates. A purse-string ligature was tied around the patella of a dog, which interfered with the blood supply. Later, osteophytes developed on the patella. These few references do not by any means exhaust the literature on this subject, but the results from various sources are in unison.

Key has discussed trauma as an etiologic factor in osteoarthritis in man. He cites instances where acute trauma has been followed by osteoarthritis. Any disturbance of posture that leads to faulty weight bearing or strain may be a factor in the development of osteophytes. He gives as examples deformities of the feet, improper alignment of fractures, unreduced dislocations and various congenital deformities. As illustrations of acute trauma leading to osteoarthritis, he mentions loose bodies or fractures into the joint. For many years Goldthwaite has emphasized posture as an etiologic factor in osteoarthritis.

The Charcot joint is an osteoarthritis. Here hypermobility and absence of the pain sense permit severe traumatism and result in a very high-grade osteoarthritis. Heiss,<sup>14</sup> made Roentgen ray exam-

inations of 159 Olympic athletes, at Amsterdam. In 23 he found periosteal thickening or osteophytes. In the football player the changes were found principally in the knee, in boxers chiefly in the elbow and wrists and in javelin and discus throwers in the elbow and shoulder. Baseball pitchers often suffer from osteoarthritis of the shoulder. A famous catcher who squats behind the bat and makes a snappy forearm throw to bases has an osteophyte on the upper third of the humerus at the tendinous attachment of a muscle, probably due to strain. The baseball finger is an osteoarthritis of the interphalangeal articulation of the distal phalanx and has the characteristics of a Heberden node.

Chronic arthritis is one of the great problems in countries where national health insurance is compulsory. A study of workers has shown that the man employed at a machine where he must frequently reach upward and pull a lever develops osteophytes in his elbow or shoulder. If he must frequently press a pedal with his foot he acquires osteoarthritis of this extremity. In England it is reported that of the various trades osteoarthritis is the most frequent in the heavy steel workers.

During the past year I have been interested in noting the frequency of Heberden's nodes in women past sixty years. Examinations of the fingers have shown that at least the majority of these individuals show some osteoarthritis. As a rule, the index finger is involved first, possibly because it is used most or more subjected to mild trauma. Where there is marked osteoarthritis of one finger, and where the other fingers are free, a history of acute trauma of the involved finger can usually be elicited. A woman, aged 45 years, showed marked osteoarthritis of the distal joint of the right middle finger, with beginning Heberden's nodes in some of the other fingers. She promptly volunteered the information that the osteoarthritis on this finger followed injury in a cash register. Another patient, a man, aged 60 years, had a high-grade osteoarthritis on one little finger, with beginning Heberden's nodes on other fingers. He related that when 6 years of age his father whipped him, one severe blow striking the distal joint of the little finger. Shortly after this the joint enlarged. Fifty years later, and probably the result of using his fingers (which is equivalent to repeated slight trauma), he developed similar changes on other fingers.

A woman, aged 35 years, for several years played a great deal of golf. At the beginning of the present season she changed her grip so that there was an interlocking of the little fingers. Within 4 months she developed a Heberden node on one little finger. Recently I saw a masseuse who had unusually marked nodes on the thumbs, with only slight changes on the fingers. She ascribed, and probably correctly, the changes on the thumbs to her custom of exerting pressure lateral to the spine.

Osteoarthritis of the knees is quite frequent in women around

50 years. It is sometimes referred to as chronic arthritis of the menopause. This is found, with rare exceptions, only in women who are overweight. In the past 2 years I have observed only 2 instances where this developed in slender women under 40 years. In both cases the trouble followed acute injury to the knee. In both of these patients one knee was injured playing hockey. Grating and pain in the joint appeared a few months after the injury. The other knee was injured in 1 patient by falling on the ice and in the other by being thrown from a horse and dragged with one foot in the stirrup. Key believes that osteoarthritis of the knees is in part due to unusual weight bearing, and in addition obesity tends to pronation of the feet and a slight valgus deformity of the knees, thus adding the factor of strain.

The spine is the point of selection for osteoarthritis. Changes here are rare under 20 years of age unless there is a history of acute trauma, which may be followed by a localized osteoarthritis; or, in case of scoliosis, when osteophytes may develop on the convexity due to unusual pressure or strain. A localized trauma of the spine, producing a fracture of a vertebra, may be followed by the outgrowth of osteophytes not only on the injured vertebra but also on the immediate adjacent vertebræ, which at most were not severely traumatized. The resulting splinting appears to be a purposeful physiologic response.

Schanz<sup>15</sup> reports the presence of a localized osteoarthritis of the spine in aortic aneurysm, with bone erosion.

Past 40 years osteoarthritis of the spine increases with each decade. Allard,<sup>16</sup> in 2000 Roentgen rays of the spine, taken at the Mayo Clinic, chiefly for a study of the urinary tract, found osteoarthritis of the lumbar spine in 67 per cent of men past 50 years and in 40 per cent of women. Men, on account of their occupations, have more opportunity to traumatize the spine. Jones<sup>17</sup> states: "Its trivial manifestations in some predynastic cemeteries are practically universal in adults and its grave ones far from rare."

There is no doubt that the frequency of osteoarthritis increases with years. Someone has said: "Age represents trauma extending over years." It is claimed that the Egyptian hieroglyphic symbol for old age is the figure of a man crippled with chronic arthritis.

Bauer<sup>18</sup> refers to the observation of Beitzkes, a German anatomist, who studied the knee and great toe joint in 200 cadavers. After 50 years of age the cartilage in 100 per cent of cadavers showed degenerative changes similar to those observed in the early stages of osteoarthritis. Weichselbaum, quoted by Bauer, claimed that the changes in osteoarthritis differed only in degree from those present in the ordinary senile individual. Smith-Petersen,<sup>19</sup> in studying the result of trauma on sacroiliac cartilage, comes to the conclusions that the changes are similar to those due to age.

Pathologic studies of osteoarthritis have been confined largely to the joints of the extremities. I was able to find but few references in the literature on the pathology of spinal osteoarthritis. As we are dealing here with fibrous cartilage, it is possible that it may react in a different manner to mechanical or chemical irritation.

Stockman,<sup>20</sup> in an article on ossifying spondylitis, refers to the "poker spine," where there is a bony encasement of the spine, rendering it immobile. These changes, he believes, are the results of chronic infection, leading to ossification of the interspinous ligaments. In this type the intervertebral disks are also ossified, as distinguished from the ordinary osteoarthritis of the spine where the disks are intact. He believes the typhoid spine falls in this group. However, as we will see later, typhoid may affect the spine in a quite different manner.

Plate<sup>21</sup> discusses the early pathology in osteoarthritis of the spine in elderly people. He states that the first change is loss of elasticity in the intervertebral disks, resulting in some thinning. Following this is evidence of bone rarefaction around the periphery of the vertebra and finally the appearance of osteophytes.

Kaufman<sup>22</sup> claims that the fatty degeneration of cartilage observed in osteoarthritis of the extremities is not usually seen in osteoarthritis of the spine. The first change in this disease, he believes, is impairment of elasticity in the intervertebral disks. It has been claimed that the lessened resiliency of the cartilage by increasing shock is a factor in the development of osteophytes. In elderly persons with spinal osteoarthritis the Roentgen ray occasionally shows thinning of the disks almost to the point of disappearance.

Jones,<sup>23</sup> in his study of ancient Nubian skeletons, has given an excellent description of the gross pathologic changes in this disease. His observations were based on a study of 6000 skeletons. He believes the very earliest change is a thickening of the periosteum at the attachment of the "anterior common ligament of the spine." This attachment is toward the upper surface of the vertebra. A small bony plate appears at this point, which is the beginning of an osteophyte. As this grows upward and touches the lower border of the adjacent vertebra, "as if in response to this new outgrowth of bone, there develops upon either side of the area of contact a bony outgrowth which fuses with the osteophyte from the vertebra below." He refers to the frequency with which the disease remains confined to one side of the body of the vertebra, and such a unilateral development may be present over great lengths of the spinal column without any signs of involvement on the other side. He further relates that the cartilage is little or not at all involved. The first appearance of the osteophyte at a ligamentous attachment suggests strain as an etiologic factor. The limitation of these osteophytes in some cases to only one-half of several consecutive vertebræ also suggests postural strain.

The evidence up to this point strongly suggests mechanical irritation as an important etiologic factor in osteoarthritis. We are not justified, however, in concluding that overuse is in all cases the sole cause.

In 1913 Frederick Muller, at a medical meeting in London, where chronic arthritis was under discussion, emphasized the noninflammatory character of osteoarthritis, and suggested changing the name to "osteoarthritis." Assmann,<sup>24</sup> who reports the above statement, has recently said that the term "osteoarthritis" is a misnomer and that "osteoarthritis" or "osteopathopathy" would be a much better term.

Osteomyelitis is recognized as a complication of typhoid fever. It involves most frequently the ribs and long bones, but occasionally the spine when it may lead to the development of an osteoarthritis.

Rugh<sup>25</sup> reported the autopsy findings in a patient dying from uremia following typhoid fever. The intervertebral cartilage between the third and fourth lumbar vertebrae was destroyed and replaced by fibrous tissue which had in part become ossified. No reference is made to the presence of osteophytes. These findings are similar to those found in rheumatoid arthritis in the extremities.

Gallus<sup>26</sup> made a study of the typhoid spine. He states that the earliest change in the vertebra is a circumscribed bone rarefaction due to infection, followed by the development of osteophytes, and later by destruction of the cartilaginous disks. He claims that the bone may be restored and the osteophytes disappear.

The question arises as to the relation of the infection to the development of osteophytes. Attention has already been called to the appearance of localized osteoarthritis of the spine after severe injury as, for instance, fracture of a vertebra, a change in which infection probably does not play a rôle. It seems quite probable that a vertebra damaged by infection might respond in the same manner as after injury by direct trauma. In each condition the development of osteophytes might be looked upon as a physiologic protective reaction. If this be true, the osteoarthritis is only indirectly due to the infection.

Hollis E. Potter recently showed me a roentgenogram of a typhoid spine. Eight months after recovery from typhoid the patient developed severe localized lumbar pain. The Roentgen ray showed slight rarefaction of a single lumbar vertebra and the presence of an osteophyte. Another osteophyte had grown upward from the adjacent vertebra below. The body of this vertebra was apparently not invaded by the infection. This response is similar to that observed from severe trauma to a vertebra, and might be considered protective in character. Ten months later the patient developed similar changes in a second lumbar vertebra. Localized changes of the same character may occur in osteomyelitis of a

vertebra, due to the staphylococcus, streptococcus or tubercle bacillus, where the damage to the vertebra is much more apparent than in typhoid infection.

Further study is needed to determine whether the infection has actually involved the adjacent vertebræ. If it can be shown that they are not involved, it would be strong presumptive evidence that the outgrowth of the osteophyte was a physiologic response or purposeful reaction, rather than directly due to the infection.

It is apparent that the pathologic changes present in osteoarthritis of the spine do not correspond to those observed in osteoarthritis of the knee. Furthermore, there appears to be several types of lesions in osteoarthritis of the spine. By far the most frequent form is the so-called senile type, which shows an increasing incidence with years. It may develop at any age following acute trauma. The only involvement of the cartilage is loss of resiliency. Here trauma is the outstanding etiologic factor.

A second type of change may be seen in osteomyelitis of a vertebra. The cartilage here is usually destroyed. It is yet to be determined whether injury to the vertebra by the infection is responsible for the growth of osteophytes, or whether they arise as a direct response to the infection.

The "poker spine" has a quite different pathology. The spine becomes encased with a bony sheath, which probably arises from ossification of the intervertebral ligament. The cartilage here is destroyed and replaced by bone, giving rise to a perfectly rigid spine. It is thought that these changes are directly due to infection.

In addition to the three forms here described further study may reveal other distinct types.

Inasmuch as pathologic studies of the joint changes in the extremities have been confined chiefly to the knee, it would be interesting to determine whether the changes in the terminal phalanges, preceding the development of a Heberden node, is of the same character. This might offer insurmountable difficulties. At least, however, the character of the cartilaginous changes in Heberden's nodes could be determined.

Nathan<sup>27</sup> injected 16 dogs intravenously with a culture of hemolytic streptococci. Six animals when killed after 8 to 90 days showed pathologic changes in the spine. In only 1 animal was it limited to the spine; the others had involvement of the joints of the extremities. On opening the spinal canal, focal areas of epidural edema were observed. The epidural periosteum was raised from the underlying bone by this edema. These changes extended into the intervertebral notches. In some areas this edematous area disappeared by absorption; in others it became organized into fibrous nodules. In 1 animal killed after 90 days two connective-tissue nodules were found near the vertebral notches of the fifth and seventh dorsal vertebræ. Such nodules, he believes, might be a



factor in causing root pain. Although no cultures were made from these edematous, other workers have found that they were sterile. If this be true, the changes were probably due to bacterial toxins rather than direct invasion. These experiments should be repeated, allowing the animal to live for a longer time, to note whether these areas become calcified.

The spur on the os calcis, wrongly considered by some as always of gonorrheal origin, nevertheless in some instances bears a direct relationship to this disease. Barr<sup>28</sup> recovered gonococci from the spur in 2 out of 5 cases. Other investigators have failed to substantiate this finding. The location of the spur at a spot where there is pressure and, in addition, traction from the plantar fascia suggests that these factors had something to do with the selection of the site for this particular gonorrheal manifestation.

Wade<sup>29</sup> has recently written a good review of this subject. He calls attention to its frequency in people with flat foot, and considers trauma from tension of the plantar fascia as an important etiologic factor. In a study of 100 cases of os calcis spur at the Mayo Clinic it was thought that occupation played a rôle, as it was more frequent in people who work standing, as, for example, barbers, dentists, motormen and store clerks.

The literature contains very few references to blood and joint cultures in osteoarthritis. Cecil was unable to obtain positive blood cultures in 18 patients with this type of arthritis.

Keys<sup>30</sup> made joint cultures from 39 patients with rheumatoid arthritis and 6 with osteoarthritis. He reported positive cultures in approximately 50 per cent of each group. He found the same microorganisms in both types. The predominating germs were a staphylococcus and a minute bacillus. These were at times found in pure cultures and at other times mixed. In 2 of the mixed cultures he found, in addition, a short-chain, nonhemolytic streptococcus. The finding of staphylococci in rheumatoid arthritis is so at variance with the experience of others that one is led to suspect contamination.

Osteoarthritis is very common in horses over 4 years of age. Webster<sup>31</sup> made cultures from the knees in a considerable number of horses, but with negative results. Hare<sup>32</sup> examined 146 horses about to be slaughtered and found evidence of osteoarthritis in 21. These horses varied in age from 6 to 28 years. After death he made cultures from the synovial fluid and synovial membrane. In 9 animals cultures were positive, but he obtained such a variety of microorganisms that he came to the conclusion that the growths were contaminative.

**Mixed Type of Chronic Arthritis.**—The presence of both rheumatoid and osteoarthritis in the same individual has been a stumbling block for everyone who has attempted to classify chronic arthritis.

We may be able to explain at least many of these mixed forms

if we accept acute trauma, long-continued mild trauma, age and strain as etiologic factors in osteoarthritis. The presence of osteoarthritis in combination with the rheumatoid type does not mean that the development of osteophytes is directly due to the rheumatoid arthritis; in other words, directly due to infection. The etiologic factor may be strain or pressure consequent to the deformity arising from muscle atrophy. A deformity of the foot due to rheumatoid arthritis might result in strain on the knee, hip or spine, with resulting osteoarthritis. I recently saw a girl, aged 17 years, greatly crippled from a rheumatoid arthritis which first appeared in early childhood. She could only move about in a crouching posture. She had a marked osteoarthritis of the spine, a condition exceedingly rare at this age except as a result of rather marked trauma.

A rheumatoid arthritis of the fingers, with deformity from muscle atrophy, may by causing unequal pressure on the rheumatoid joint lead to the formation of osteophytes.

The individual past 50 years who develops a rheumatoid arthritis probably has already an osteoarthritis of the spine and possibly Heberden's nodes. I have seen several cases of this sort. A patient at any age who develops a rheumatoid arthritis may have previously had a localized osteoarthritis from acute trauma. The pathology of the two types of arthritis speaks very strongly against a common etiology.

**Conclusions.** Chronic rheumatic joint disease—pathologically, etiologically and clinically—may be divided into two types.

Pathologically, the joint changes in rheumatoid arthritis are inflammatory; in osteoarthritis degenerative.

Etiologically, rheumatoid arthritis is usually and probably always due to an infection. Etiologically, trauma, in the broad sense of the word, is the chief, if not the sole, factor in osteoarthritis of the extremities. It is probably the most frequent factor in osteoarthritis of the spine. Here, however, the pathologic changes are quite different from those observed in the extremities and the possible rôle of infection in certain types cannot be ruled out. For the noninfective type "osteoarthrosis" is a more fitting term than "osteoarthritis."

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## THE SIGNIFICANCE OF THE GASTRIC SECRETIONS IN PERNICIOUS ANEMIA.

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THE significance of achylia gastrica in pernicious anemia has long been under dispute. The recent work of Castle, however, has indicated that the gastric disorder may be the primary factor in the production of the disease. He demonstrated that typical remissions, similar to those produced by liver, could be induced by the daily administration of 200 gm. of raw beef, previously digested in normal gastric juice, either in the stomach<sup>1</sup> or *in vitro*.<sup>2</sup> Neither the beef nor the gastric juice was effective alone, nor were the two when fed separately. From these experiments, Castle suggested that pernicious anemia is a deficiency disease of a new type, caused by lack of an unknown substance produced from protein during the course of normal digestion, the production of which, however, fails to take place in the deficient gastric juice of pernicious anemia. He, therefore, regards the achylia gastrica as the essential pathologic process. This theory explains remissions following the eating of

liver or kidney by assuming the presence in liver and kidney of the preformed effective substance which does not have to be set free by digestion.

There are several difficulties in the way of a complete acceptance of Castle's theory. First, it fails to explain the spontaneous remissions so characteristic of the untreated disease, during which, as far as we know, there is no change in the character or composition of the gastric juice. Second, it is known that complete gastric achylia may persist for years in apparently healthy people, without the development of any of the evidences of pernicious anemia. Finally, it does not account for the occasional rare patients with blood pictures identical with those of pernicious anemia, who respond typically to liver therapy, but whose gastric juice appears to be entirely normal. That gastric juice which is apparently normal should entirely lack some unknown factor necessary for the activation of the effective substance in beefsteak seems *a priori* to be unlikely, but Castle has recently shown this to be the case. He found that gastric juice obtained from 2 patients with "pernicious anemia" was normal as to its content of acid, pepsin and rennin, but failed, after incubation with beefsteak in the usual way, to produce the substance effective in causing remissions in other cases of pernicious anemia.<sup>3</sup> He assumed, therefore, the presence in normal gastric juice of some unknown factor which did not seem to be present in the juice from his pernicious anemia patients, even though the secretions of the latter seemed normal in every other way.

A finding as striking as this obviously requires confirmation. An opportunity recently presented itself when there were available simultaneously 2 patients, 1 with pernicious anemia and 1 with sprue, both of whom had apparently normal gastric juice and both of whom had responded typically to liver therapy. At the same time there was available a fresh case of typical pernicious anemia upon which the digested material could be tested. As will be pointed out, our observations failed to confirm those of Castle.

**Experimental Observations.** The experiment consisted, as pointed out above, of the feeding to a patient with typical Addisonian pernicious anemia, of beefsteak, previously digested in the gastric juice of other patients with the blood picture resembling that of pernicious anemia, who had previously responded to liver in the usual way but whose gastric secretion appeared entirely normal. The gastric juice was obtained from 2 patients:

CASE 1.—J. G. was a case of sprue who had responded to liver, whose record was previously reported by Bloomfield and Wyckoff.<sup>4</sup> His gastric juice was used only for the first two doses.

Juice for the rest of the experiment was obtained from the other patient, suffering from pernicious anemia, whose clinical record is here included to make clear the nature of her case.

CASE 2.—C. M., aged 43 years, a Central American housewife, entered the hospital on May 9, 1925, complaining of indigestion and occasional

diarrhea. Her family history and past history were unimportant. For 10 years she had been troubled with acid eructations, gas and occasional epigastric pain after meals. She was ordinarily constipated but had frequent attacks of mild diarrhea lasting two or three days. Her appetite had been poor for 1 year and she had been weak and tired for 3 months. Her mouth was sore and her ankles became slightly swollen at times.

On examination she was fairly well nourished and did not appear ill. The tongue was pale and smooth. The posterior cervical glands were slightly enlarged. The heart and lungs were negative. The liver and spleen were both palpable just beneath the costal margin. The extremities were negative. The blood count was: Red blood cells, 1,810,000; hemoglobin, 54 per cent (Sahli); color index, 1.75; white blood cells, 5450; polymorphonuclears, 75 per cent; lymphocytes, 24 per cent. The smear showed moderate poikilocytosis, marked anisocytosis, polychromasia, Howell-Jolly bodies and a few normoblasts. An Ewald test meal gave a total acid of 48 degrees and a free hydrochloric acid of 40 degrees, 90 minutes after the meal.

She was discharged, without a definite diagnosis, on Fowler's solution and iron cacodylate. This treatment was continued for two months in the Outpatient Department. She improved subjectively, and the red blood cells increased to 2,890,000 and the hemoglobin to 65 per cent. No cause of the anemia was found on very careful study.

She did not return until she again entered the hospital on April 15, 1930, complaining of indigestion. Her condition during the interval had remained much the same. Her gas, eructations and epigastric pain persisted. She felt quite well at times and at other times was weak and tired. For the last year she had been quite weak and had lost 30 pounds in weight.

The physical examination was unchanged except that the liver and spleen were not felt. Vibratory sensation was normal. The blood count was: Red blood cells, 2,200,000; hemoglobin, 58 per cent (Sahli); color index, 1.3; white blood cells, 6400. The smear showed anisocytosis, poikilocytosis, polychromasia and normoblasts. The icterus index was 11.2 and the indirect van den Bergh 2 units. Gastric analysis after histamin gave:

		histamin				
Time . . . . .	Fasting	↓	10'	20'	30'	40'
Total acid . . . . .	5°		10°	20°	68°	84°
Free hydrochloric acid . . . . .	0		0	7°	58°	72°
Volume in cc. . . . .	26		20	22	60	52

A diagnosis of atypical primary anemia was made, and she was placed on ventriculin, 2 vials daily. There was no change in her blood after 10 days, and liver extract (Lilly 343) was substituted for ventriculin in doses of 3 vials daily for 2 days and then 6 vials daily for 16 days. The reticulocytes increased to 9.5 per cent on the tenth day of liver therapy and the hemoglobin rose to about 80 per cent. The red blood count rose to about 3,000,000 after 40 days, as shown in Chart I. She continued to take liver at home and on July 17, 3 months after treatment was started, the red cell count was 4,000,000 and the hemoglobin 76 per cent. She was clinically much improved.

This response was characteristic of that obtained in pernicious anemia. Because of the high initial level of the red cells, a high reticulocyte count or a rapid improvement in the blood could not be expected, as was shown by Minot.<sup>5</sup>

**Method.** The method used in preparation of the material for feeding was that described by Castle and Townsend.<sup>2</sup> Gastric juice was obtained from Cases 1 and 2 after histamin stimulation, a dose of about 0.7 mg. being given after aspiration of the fasting contents and again after 40 to 60 minutes.

Aspiration was continued until approximately 300 cc. of juice had been secured, and all of it was used each day. The juice contained an abundance of acid. The lowest values in the complete specimens were: Case 1: free hydrochloric acid, 42 degrees; total acid, 70 degrees. Case 2: free hydrochloric acid, 40 degrees; total acid, 55 degrees. The highest value obtained from Case 2: free hydrochloric acid, 90 degrees; total, 110 degrees. The juice was obtained daily and used immediately. It was first filtered through gauze and mixed with 200 gm. of finely ground beef muscle in a large beaker. It was then titrated with concentrated hydrochloric acid to a pH of about 3 (estimated by the production of a distinct red color when a drop of the mixture was added to a small amount of distilled water containing a drop of para-dimethyl-amino-azo-benzol), and placed in an

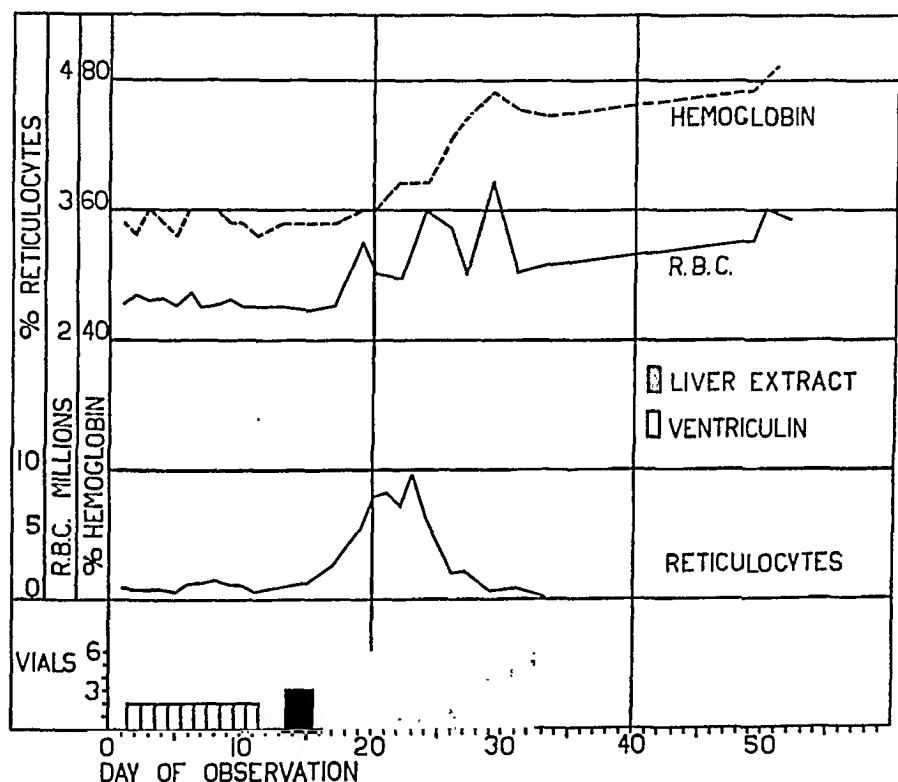


CHART I.—Blood response of a case of "pernicious anemia" with normal gastric juice to ventriculin and liver-extract feeding.

incubator at 37° F. for 2 hours. The mixture was stirred at frequent intervals and the pH maintained by additions of hydrochloric acid when necessary. At the end of the incubation period the mixture was strained through a fine wire sieve and the liquid portion was brought to a pH of about 5 with 5N.NaOH. This was done by titration to about the middle of the range of methyl red. The neutralized material was then introduced, through a stomach tube, into the fasting stomach of Case 3.

**Experimental Data.** The clinical record of Case 3, used for testing the potency of the digestion mixture, is briefly as follows:

**CASE 3.**—M. A., aged 55 years, an American housewife, entered the hospital on May 30, 1930, complaining of weakness for 3 years. Her family history and past history were unimportant.

For 3 years she had had intervals of weakness, often with swelling of the

feet, alternating with intervals in which she felt quite well. During this same period she had noted a marked pallor. Her tongue was sore at times. For two years she had had numbness and tingling of her legs, at times severe enough to make walking difficult. She had lost no weight.

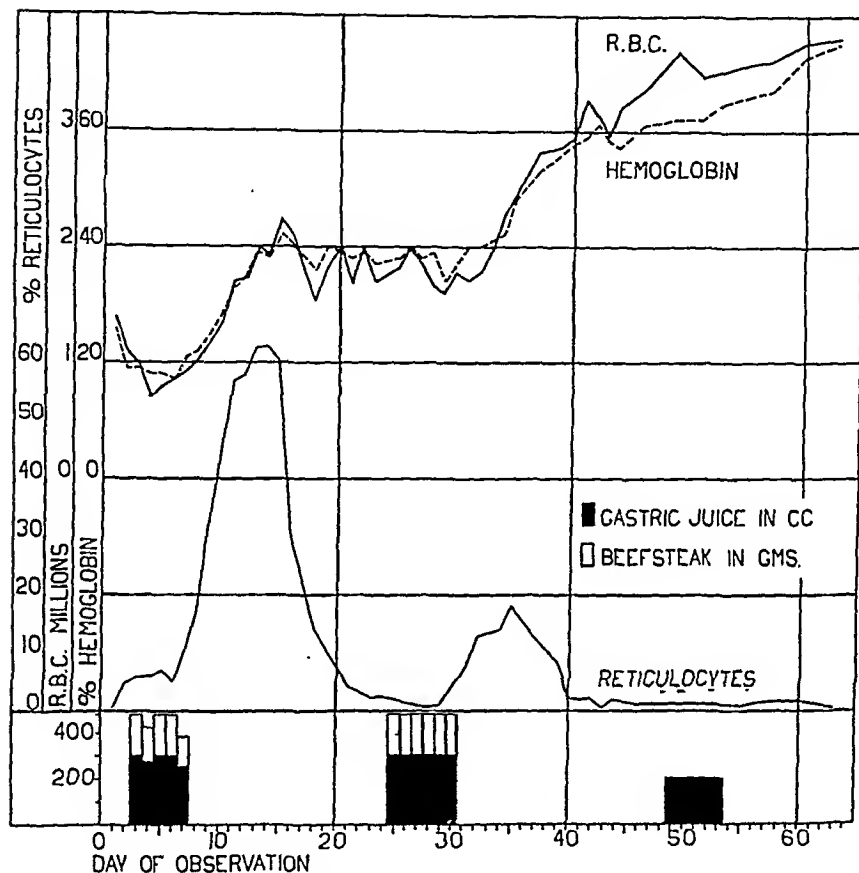


CHART II.—Blood response of a case of pernicious anemia, receiving a mixture of beef and gastric juice from "pernicious anemia" patient reported in Chart I.

On examination she was extremely pale and sallow, but, although rather poorly developed, she was quite well nourished. The tongue showed a practically complete papillary atrophy. The heart was negative and the lungs were normal except for diminished breath sounds at the right base. The spleen was palpable 3 cm. below the costal margin. The reflexes were normal, but joint sensibility was diminished and vibratory sensibility was absent in both legs. There was moderate pitting edema of the ankles. The blood on the third day was: Red blood cells, 700,000; hemoglobin, 18 per cent (Sahli); color index, 1.3; white blood count, 2350; polymorphonuclears, 42 per cent; lymphocytes, 48 per cent; eosinophils, 4 per cent; basophils, 1 per cent; neutrophilic myelocytes, 5 per cent. The reticulocytes made up 6 per cent of the red cells. The smear showed moderate anisocytosis and poikilocytosis, with occasional macrocytes. There were a few cells showing polychromasia and stippling. The icterus index was

13 and the indirect van den Bergh 2 units. Gastric analysis after histamin gave no free hydrochloric acid and the highest 10-minute volume was 4 cc.

This case presented all the cardinal features of pernicious anemia and was an excellent one for determining the potency of the digested beef because of the extremely low red cell count and hemoglobin. The course of her response is shown in Chart II. Because of the severity of her disease, a prolonged control period was considered inadvisable and therapy was started on the third day. According to Minot,<sup>5</sup> the first 4 days of treatment may be safely included in the control period, since this length of time is always required before any response takes place. We have, therefore, a control period of 7 days. During this time the red cells and hemoglobin fell slightly and the reticulocytes remained at about 6 per cent. On the fifth day of therapy the reticulocytes had risen slightly and the sixth day they were 17 per cent, so treatment was stopped. They continued to rise, however, and on the twelfth day reached the extremely high value of 63 per cent. Almost simultaneously with the reticulocyte response the red cell count and the hemoglobin increased, the former by a little over 1,000,000 and the latter by slightly over 20 per cent, where they reached a very definite level. The reticulocytes rapidly fell to below 1 per cent.

Because of the high initial reticulocyte level and the magnitude of the response, the possibility that we were observing a spontaneous remission was considered. To decide this question, the treatment was repeated after the blood had maintained a distinct level for 10 days. This period, together with the first 4 days of therapy, gives a second control period of 14 days. Following the second series of feedings, there was another typical response, the reticulocytes rising to 18 per cent and the red cells and hemoglobin by about the same amounts as observed after the first treatment. During the experiment the patient was, of course, on a diet free from liver and kidney.

During the first series of feedings, due to an oversight, Case 2 was receiving 250 gm. of liver daily, and the first time her juice was used (*i. e.*, for the third dose) she had had this amount 3 hours before aspiration. Since the fasting contents of the stomach were removed and discarded, the actual amount of liver substance transferred to Case 3 must have been extremely small. On each of the 2 subsequent days at least 20 hours elapsed between her liver meal and aspiration. During the second series of feedings she was on a liver-free diet.

Eight days after the reticulocytes had dropped to normal and when the red cell count and hemoglobin had reached an approximate level a series of five daily feedings of 200 cc. of gastric juice from Case 2 was given, without beefsteak, as a control. Following this there was a slight rise in red cells and hemoglobin but no increase in reticulocytes.

**Discussion.** The character of the response, its time of occurrence and the fact that it could be obtained repeatedly leave no doubt but that in this case the material used was highly potent. The results cited are certainly not in accord with the hypothesis proposed by Castle that pernicious anemia is dependent upon the gastric defect, for the gastric juice of Case 2, typical of pernicious anemia except for gastric secretion, was able to produce from beef muscle a material which caused typical remissions. The results are also opposed to those obtained by Castle, in whose cases, as we pointed out above, the "activating principle" was not demonstrated in otherwise normal juice.

Since the gastric juice of Cases 1 and 2 is able to produce this



antianemic substance, it is, perhaps, remarkable that these patients did not produce remissions in themselves. That they have not merely recovered a normal secretion is demonstrated by the fact that they both require liver to keep their blood in a relatively normal condition. The constituents of their diets while they were anemic are not known, but it is possible that if they had taken large amounts of raw beef they might have had remissions. Another possibility that suggests itself is that only the powerful stimulus of histamin will cause a sufficient secretion of the hypothetical substance which produces an antianemic factor from protein. The treatment of sprue and pernicious anemia with raw beef, accompanied by subcutaneous injections of histamin, would prove or disprove this possibility.

The control experiment in which gastric juice alone was fed is not conclusive. There was a slight increase in red cell count and hemoglobin, but not of the magnitude observed after the digested beef. Moreover, when this therapy was started the blood was still improving slightly. The absence of a reticulocyte response is of no significance because of the high level of the red blood cells at this time and also because a second or third reticulocyte response only follows the administration of a larger dose of the effective substance than the dose that produced the primary response.<sup>5</sup> Wilkin-son<sup>6</sup> obtained slight reticulocyte responses from feeding normal gastric juice, but he fed it with meals containing protein, so that the response may well have been due to interaction between the juice and the protein rather than to the juice alone.

We do not believe that the significance of the achylia gastrica in pernicious anemia is as yet entirely clear, and the subject requires much further study. Certainly, in view of the rarity of cases presenting the clinical features of pernicious anemia without the characteristic achylia, the accumulation of a large series of experiments of this sort is a tedious matter, but in view of the contradiction between our results and those of Castle, it is evident that further similar cases must be studied before final conclusions can be drawn.

**Summary.** 1. The treatment of a patient with pernicious anemia by daily feedings of beef muscle, predigested in the gastric juice of another patient with all the clinical features of this disease except for the achylia gastrica, is reported. An unusually brilliant response resulted.

2. To rule out the chance of a coincident spontaneous remission, the treatment was repeated, after the blood had assumed a constant level, with similar results.

3. Gastric juice alone failed to give a definite response.

4. The bearing of these results on the theory that pernicious anemia is directly dependent on a defect in gastric secretion is discussed.

NOTE.—Since this paper was submitted for publication, on August 29, 1930, another paper by Dr. Castle has appeared in the *AMERICAN JOURNAL OF THE MEDICAL SCIENCES* for September, 1930. In this paper he anticipates the results just reported and suggests that the explanation might be in a failure of absorption of the effective substance even though properly formed. The adequacy of absorption in our 2 cases has been amply demonstrated, at least as regards liver extract and liver, by their previous therapy, although the possibility of failure to absorb effective substance released from beefsteak has not been excluded.

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### POLYPI AND POLYPOID CONDITIONS OF THE GASTROINTESTINAL TRACT.

WITH SPECIAL REFERENCE TO PATHOLOGIC AND RADIOLOGIC  
ASPECTS.

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A REVIEW of the gradually increasing literature on benign tumors of the stomach and intestinal tract, reported under various titles such as gastric and intestinal polypi, adenomata and polyadenomata of the stomach, gastric and intestinal polyposis, gastritis and colitis polyposa and inflammatory adenomatoid hyperplasia of the gastric and intestinal mucosa, makes it evident that a clearer differentiation of the pathologic condition in a given case and its assignment to its proper group should be made preliminary to a discussion of etiology, incidence, symptomatology, radiologic diagnosis or clinical course.

As many authors have pointed out, the term polypus as used clinically does not connote a homogeneous group and, therefore, has no precise pathologic significance; it is an anatomic or morphologic term applied to a form of growth arising from any of the tissues constituting the walls of the stomach or intestines, or at times from embryonal rests therein. Thus fibromata, hemangiomata, papillomata, adenomata, neurofibromata, lymphangiomata, lipo-

mata, cysts and mixed tissue tumors, have all been found at autopsy or at operation as polypoid growths projecting from the inner or outer coat of the gastrointestinal tract. They may occur either in the stomach or intestine alone or at times in both, and it is important to recognize their similarity in genesis and structure in the two locations. Kaufmann and Hauser observed polypoid involvement of the whole gastrointestinal tract from the cardia to the anus, though the stomach and the large bowel are the situations most frequently involved. When they develop from or beneath the mucous coat, traction during peristalsis apparently is a factor in producing the polypoid form of tumor. They vary in size from growths as small as lentils or peas, in all graduations up to a fetal head; in number they vary from a single growth to as many as 300 or more; they occur at all ages, from childhood onward, but have most frequently been found in persons from 40 to 50 years of age, though presumably their origin was many years earlier. Dieulafoy has remarked that multiple polypi are usually of the same size in a given case, arising as if by simultaneous eruption.

In the stomach they are most frequently found toward the pylorus; they may cover a considerable area or sometimes nearly the whole interior of the organ. Single or multiple polypi may exist for many years without symptoms, and even if symptoms appear they are often due to accidental or mechanical causes or to coincidental disease.

Thus, a number of cases have been reported (Cornil, Chiari, Myer, Cleghorn, Sutherland) in which a gastric polypus has been forced into the pylorus or duodenum, producing partial or complete obstruction, or by traction on the gastric wall has caused intussusception (Chiari, Collier, Wade, Eliason and Wright) of the stomach into the duodenum. Of Balfour and Henderson's 58 cases 10 per cent gave a history of pyloric obstruction, usually intermittent. Cholecystitis associated with gastric polypi has frequently been reported, also pyloric ulcer (Sutherland) and 2 cases of rupture of the duodenum, where a gastric polypus has passed through the pylorus. Cases 2 and 3 reported in this paper gave histories of duodenal ulcer. One of us (Anderson) saw a patient with Dr. G. W. Ross and Dr. A. S. Moorhead, in 1922, a woman, aged 42 years, complaining of severe stabbing pain above and to the right of the navel coming on suddenly after breakfast, lasting for an hour and then disappearing until the following morning. Later the abdominal pain became more continuous and associated with persistent vomiting. At operation a small myxomatous polypus was found projecting from the mucous membrane of the upper part of the jejunum and producing intussusception. Excision of some 5 inches of the involved bowel and end-to-end anastomosis was followed by an uneventful recovery.

As a rule, the symptoms produced by polypi are not continuous

or progressive, as one might anticipate, but rather long periods of quiescence may intervene. The disappearance of symptoms may be due to the subsidence of an associated disease, such as cholecystitis, or to the fact that mechanical symptoms (swelling, volvulus, intussusception, pressure) are not necessarily continuous.

Gastric polyps did not escape the attention of Morgagni, though Cruveilhier has priority (1829) in having recognized more fully the nature of the condition. In his opinion gastric polypi were not rare; they were usually multiple, either sessile or pediculated; originated from the otherwise unaltered mucosa; were found in the intestine as well as in the stomach; in 1 of his cases intussusception and in another pyloric obstruction occurred; they might be present without symptoms; in 1 case cancerous transformation had occurred in one of a group of multiple polypi.

Andral differentiated them from cancerous growths. Rokitansky, in his experience of over 30,000 autopsies, observed cases of gastric polypus, and states the mucous membrane may sometimes be warty and rugged from the increase in size of their papillæ and follicles, and that various duplications and prolongations may occur consisting of two varieties of permanent inequality—the mucous or cellular polypus and the vesicular polypus. He grouped them with similar polypoid growths in the nasal cavities, the large intestine, bladder and uterus, and believed they were the result of inflammatory irritation, though a congenital factor might exist in some cases. He also recognized that malignant transformation may take place.

Ebstein (1864) divided gastric polypi into the pedunculated and nonpedunculated; into those occurring in groups and those in isolated growths. Brissaud (1885) classified polypi as polyadenomata, but this term is correct only insofar as it is applied to benign tumors arising from mucosal epithelium.

Ewald described polypoid growths as a result of chronic gastroadenitis. He refers to a drawing of Cruveilhier's "in which the polypoid growths hung down from the mucous membrane like the teats of a young puppy."

Chiari (1888) reported a case of gastric intussusception due to a group of polypi near the pylorus escaping through the opening into the duodenum and producing partial obstruction. Cornil also reported a case of pyloric obstruction. In Myer's case a mass of polypi obstructed the pylorus and the patient died from hemorrhage 3 days after their removal by operation. As they are quite vascular, it is readily understood that they may swell when subjected to irritation or constriction.

Ménétrier's investigation of gastric polypi, published in 1888, marked an important step in advance. He accepted Brissaud's designation of polyadenomata and divided them into two classes: (a) *Les polyadenomes polypeux*, which he believed developed from

the superficial; (b) the flat or fanshaped *polyadenomes en nappe*, which developed from the deeper portion of the glands. He believed they were the result of chronic gastritis.

Before considering the etiology, pathology and clinical course of the two classes of polyadenomata described by Ménétrier, it should be emphasized that benign polypi of the gastrointestinal tract, arising from other tissues than the superficial or the gland epithelium of the mucosa, should be excluded from the discussion. If we accept the contention of Borrmann and others, the single adenomatous polypus should be included in the same group as the multiple, as they arise in the same way and show a similar tendency to carcinomatous transformation, and the papillomatous polypus would also be included as it arises from mucosal epithelium. The polyadenomata, then, would constitute a definite group of epithelial origin, arising from or under the mucous membrane, exposed to the irritations and inflammatory reactions affecting the mucous membrane, and further characterized by their liability to undergo cancerous transformation. The only thing they have in common with other benign polypoid tumors is their liability to produce certain mechanical symptoms, as has already been mentioned. Moreover, the myomata, fibromata, lipomata and other tumors, not of epithelial origin, more often project from the outer than from the inner walls of the gastrointestinal tract, so that inflammatory irritation of the latter obviously does not enter into the question of their causation as it does with polypi of epithelial origin.

In discussing the polypi of epithelial origin—the solitary and multiple adenomatous polypi and the papillomata—it is necessary to consider their causation and their relationship to inflammatory hyperplasia of the mucous membrane.

In common with most of the older writers, Ménétrier believed that gastric polyadenomata are the result of chronic gastritis and the inflammatory origin is still upheld by many authorities, including Ewing, Hektoen and Riesman, Versé, Konjetzny, Lubarsch, Hauser and other pathologists. Clinicians have inclined to the inflammatory theory, as suggested by the terms gastritis and colitis polyposa.

Others, following the teaching of Cohnheim, emphasize the importance of congenital tissue rests, or *anlage*, or perhaps some hereditary abnormality of the epithelium. They bring forward many arguments against the inflammatory theory, among others the occurrence of polypi in the comparatively young when there has been no antecedent inflammation; the existence of polypi for many years without symptoms; the frequency of chronic inflammatory conditions involving the gastrointestinal mucous membrane without polypoid formation; that chronic gastritis, as a rule, tends to atrophy rather than to hyperplasia of the glandular tissue; that

in solitary adenomatous polypi the growth arises abruptly from the mucous coat without evidence of inflammatory reaction in the surrounding tissues, and that the type of epithelial reaction and its relation to the underlying connective tissues in true adenomatous polypi differs from that of inflammatory hyperplasia. They maintain that the inflammatory reaction associated with adenomatous polypi may be a secondary phenomenon due to irritation produced by the growth.

On the other hand, some authorities who emphasize the paramount importance of the congenital factor admit that inflammatory irritation may act as an exciting or releasing cause for producing tumor activity in tissue rests. A Brunnerian type of polypus of the stomach has been described by Hayem, consisting of a glandular structure analogous to that of the duodenal glands. Konjetzny and Versé claim to have traced a direct and gradual continuity from chronic gastritis to mucous membrane hyperplasia, polyposis and cancer. In 12 cases of early gastric carcinoma found incidentally at autopsy in patients dying of other diseases Versé noted flat or papillary or polypoid thickening of the mucosa, and in several of them hyperplastic or atrophic gastritis. Ewing attaches slight importance to developmental anomalies, and states that in some cases carcinoma is associated with general hypertrophic gastritis, in others with a focal gastritis. Hayem describes diffuse scirrhous carcinoma developing from a diffuse parenchymatous gastritis, and cancer is known to develop frequently in the scars of gastric ulcer. Fibiger and Wassink claim to have produced gastric polyposis by the experimental feeding of a species of nematode, and Ishibashi and Otani by the application of coal tar. In Dukes' experiments with the application of tar to mice the sequence, though not invariable, was hyperplasia, papilloma, epithelioma.

Both the congenital and the inflammatory factors appear to be important and may be coördinated by accepting the one as a primary and the other as a releasing factor. Those who accept this view believe that inflammatory irritation can produce adenomatous polypi only in the presence of epithelial rests, and that inflammatory hyperplasia of the mucous membrane and the type of polypoid condition ordinarily accompanying it should be considered a different type of formation from that of true adenomata. Börsch and other authorities, however, admit the difficulty of sharply differentiating the two conditions. Whether acting primarily or secondarily, it is probable that inflammatory irritation is very important in its relation both to the adenomata and carcinomata.

Seherer, from a study of 4 cases of massive folding of the gastric mucosa (*Riesenfaltenbildung*) found incidentally at autopsy, emphasizes the congenital factor, often associated with developmental defects or anomalies in other parts of the body: "Es handelt sich bei unseren Falten demnach um echten kongenitalen

partiellen Riesenwuchs." Inflammation and nervous or hormonal influences, he believes, may be releasing factors.

Gastric adenomatous polypi occur more frequently than has been supposed, even though many recent textbooks and systems of medicine do not mention them. Osler states that gastric polypi (polyadenomata) are common. Ebstein reported 14 cases of gastric polypi, 12 single and 2 multiple, in 600 autopsies. Eliason and Wright, in 8000 autopsies in the Philadelphia and University of Pennsylvania Hospitals, state that polypi were found in 32 per cent of gastric tumor cases, though only 1 case of polyposis was observed. Other pathologists and clinicians have found gastric polypi much less frequently. Thus Tilger reports only 14 cases in 35,000 autopsies; Chrosrojeff, in the Obruchow Krankenhaus, 4 cases in 7500 autopsies; Meulengracht, of Bremen, 11 cases in 11,475 autopsies. In the Mayo Clinic Balfour's case was the only one observed in 8000 gastric operations up until 1919, and Carman had recognized only 2 cases in 50,000 radiologic examinations; but Balfour and Henderson, in 1927, reported 58 cases of benign tumor of the stomach, 14 of which were fibroadenomatous polyps, 4 adenomas, 1 papilloma, 4 cases of polyposis and 2 of hypertrophied mucosa.

Dukes carefully examined 127 intestines from cecum to sigmoid and found simple tumors in nearly 10 per cent, and in 33 consecutive cases of cancer of the rectum adenomatous tumors were found in 25.

It is evident that exclusion of the polypoid growths of hyperplasia from the adenomatous group will be reflected in the statistical estimations of various authorities. Those who include the inflammatory polypoid growths of hyperplasia will find polypi comparatively frequently, while those who include only the true adenomatous polypi will find them rarely. The diversity of opinion among authors as to frequency is, therefore, accounted for by the conditions which different observers include within the term polypi or polyposis. Brunn and Pearl succeeded in collecting 84 cases of gastric polyposis up to 1926, and several others have been reported since that time.

In an experience of some 2000 autopsies in Toronto in hospital and private practice, one of us (Anderson) has met with a case each of multiple cysts of the stomach and intestines, *polyadenoma en nappe* of the stomach, benign adenoma of the duodenum, myxoma of the upper part of the jejunum, 1 of lipoma and 1 of myoma of the outer wall of the colon; 3 cases of polyposis of the colon and 1 of a large adenomatous polypus of the rectum in a boy, aged 17 years, producing obstruction.

Wegele made the first antemortem diagnosis of polyposis ventriculi at operation, in 1909, and Balfour's case was the first diagnosed by radiographic examination. In 1913 J. A. Myer reported a case in America in which he encountered at operation a mass of

polypi producing pyloric obstruction; in 1921 Alex. Macphedran reported a case of gastric polyposis in a woman, aged 50 years, who had suffered for years from epigastric discomfort after meals, diagnosed by radiographic examination (Dr. Dickson). Schindler, of Munich, reported a case, in 1922, diagnosed by gastroscopy.

The fact that polypi may exist for many years without symptoms, or with symptoms of digestive disturbance neither definite, characteristic nor uniform, probably accounts for their frequently being overlooked. As a rule, no tumor mass can be palpated, though there may be a sense of increased resistance over the epigastrium. Even at operation the condition may not be recognized unless the stomach is opened and its interior explored. How readily this may occur is illustrated by a patient, a woman, aged 40 years, who had suffered for years from symptoms suggestive of duodenal ulcer. Her abdomen had been opened on two occasions by experienced and competent Toronto surgeons and nothing found. Dr. L. G. Cole, of New York, after radiographic examination, concluded she had gall stones, though the clinical evidence pointed more to the duodenum as the seat of the trouble. As she suffered from intermittent obstructive symptoms she was referred to Dr. H. A. Bruce, in 1914, for operation and investigation of the gall bladder duodenal area. He found a shaggy, adenomatous tumor, 12 cm. long, 7 cm. wide and 3 cm. thick, attached to the interior of the first part of the duodenum by a thin pedicle some 5 cm. in width. (Fig. 1.)

The mass was easily removed and the patient made an excellent recovery. The radiographic plates in this case were misleading from the fact that the barium, caught in the interstices of the tumor threw shadows simulating multiple biliary calculi. An interesting feature of this case was the intermittent character of the symptoms, exacerbations evidently being due to occasional vascular engorgement and swelling of the tumor producing partial obstruction.

As the gastrointestinal adenomatous tumors eventually undergo carcinomatous transformation in 45 to 60 per cent of cases (Doering, Wechselmann, Meulengracht), no doubt the condition has often been mistaken for primary carcinoma. Mills, however, found malignant degeneration in only 20 per cent of 20 cases, and Brunn and Pearl in only 12 per cent of their collected cases. These percentages, like other statistical figures, will obviously vary with the conditions included within the term polypi or polyposis. Stewart, in 11,000 autopsies in Leeds General Infirmary, found gastric polypi in 47 and 13 out of 263 cases of cancer of the stomach, or 4.9 per cent, originated in polypi.

The symptoms associated with polypi will vary according to their size, number, location and structure, and also in relation to preceding or associated diseases. The mechanical symptoms are produced especially by pressure, traction and partial or complete



occlusion of orifices or lumen of the tract and may be intermittent or continuous.

In the small number of adenomatous gastric polypi reported, absence of free hydrochloric acid has been a prominent symptom and this is suggestive of widespread changes in the glands such as occur in gastritis with atrophy. As polypi may exist for years without symptoms, we have no knowledge as to how early the achylia develops; it is not a constant symptom, and one would scarcely expect to find it in the case of single or few polypi with otherwise normal mucosa. Cases with achylia may present an intractable diarrhea. These considerations apply equally to the presence of egg-white mucus in the stomach contents, which has frequently been referred to as a symptom of polyposis. Severe hemorrhage or occult bleeding has been noted in some 40 per cent of cases and is similar to that occurring in papillomata of the bladder.

Anemia is usually mentioned as an important symptom and may be explained by loss of blood, interference with digestion or atrophic changes in the glands. Balfour and Henderson emphasize its importance and refer to 1 case diagnosed as pernicious anemia. In 3 out of 8 cases which had undergone carcinomatous transformation, reported by Miller, Eliason and Wright, a diagnosis of pernicious anemia had been made.

Microscopic examination of pieces of tissue obtained from stomach contents or feces may assist in diagnosis, though this measure is uncertain unless the tissue is large enough to show submucosal infiltration.

As pointed out by Carman, Ruggles and others, radiologic examination is not an infallible means of diagnosis, though undoubtedly it is the most important. It is likely to be of most value where the polypoid condition is widespread, deforming the gastric outline or associated with obstructive symptoms. Ruggles (quoted by Brunn and Pearl) states: "Just as in the pathologic picture, so in the roentgenograms there are borderline cases in which one cannot differentiate between hypertrophic rugæ resulting from chronic gastritis and polyposis." It is of value in the diagnosis of ulcer, gall stones and other associated conditions, and no doubt will be of assistance more frequently in the future than it has been in the past. It is of less use in the case of solitary polypi, especially if not causing mechanical symptoms or before carcinomatous transformation.

According to Moore, "Multiplicity of the growths, as evidenced by multiple internal filling defects, is strongly indicative of benignity. In classic examples of diffuse polyposis the gastric shadow *has the appearance of a coarse sponge*, because of the numerous oval or rounded translucences. The stomach is of normal size, the line of the curvatures is usually traceable, *although it may be serrated*, and

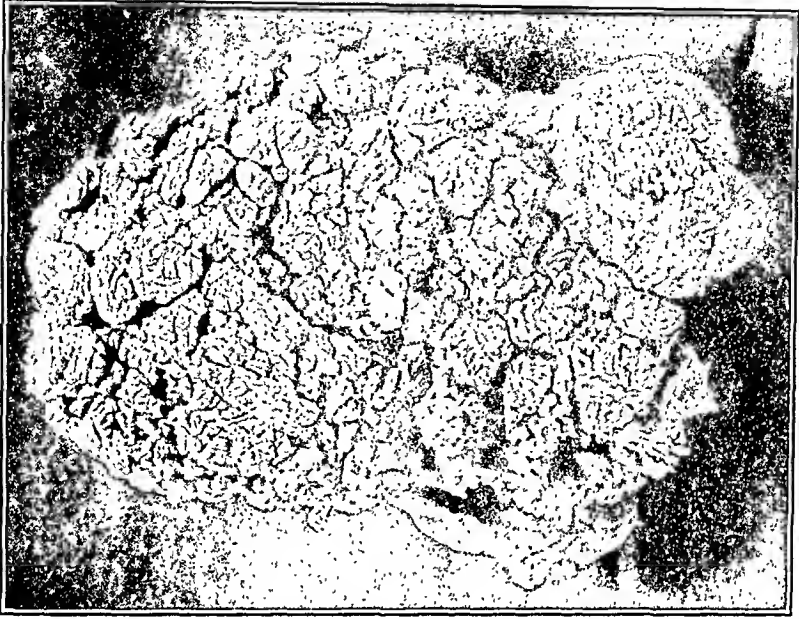


FIG. 1.—Pediculated adenoma of the duodenum.



FIG. 2.—Case 1. R. L. M., aged 49 years, Gastric polyposis.



FIG. 3.—Case 2. Mrs. H. W., aged 54 years. Suspected gastric polyposis.



FIG. 4.—Case 3. Mrs. G. B., aged 37 years. Suspected gastric polyposis.



FIG. 5.—Leukemic deposit in the stomach wall, presenting gross appearance of polyadenoma en nappe.

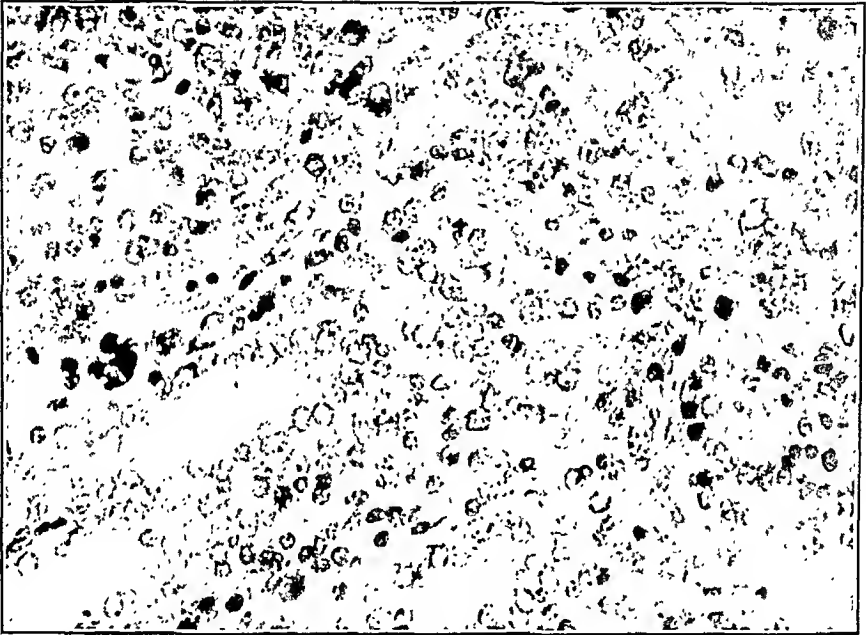


FIG. 6.—Histologic section of leukemic stomach.

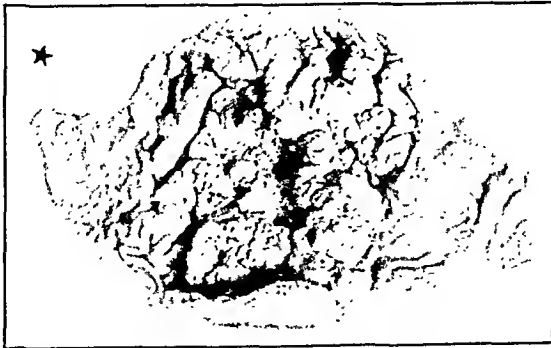


FIG. 7.—Adeno-carcinoma of the stomach developing in the center of an area of polyadenoma en nappe.



peristalsis runs its ordinary course. As a whole, the picture is striking and distinctive."

The cases reported in this paper present an interesting and generally uniform series of radiologic findings. On the screen the greater curvature showed serrated irregularities which could be obliterated by pressure, yet this pressure caused more pronounced irregularities in different portions due to the barium being forced in between the rugæ, and, further, with the patient placed in different positions and no pressure exerted, other irregularities were observed. Peristalsis was noted to pass through the involved areas, though somewhat diminished, especially so in Case 1 (Fig 2). No palpable mass could be felt, yet in Case 1 a soft fullness was elicited over the involved area. The plates all showed the same serrated irregularities as described on the screen with the addition that variations of density and irregular streakings were noted in the adjacent parts of the stomach. This mottling and streaking and serrated contour varied on the different plates of the same series. All showed a ground wave of peristalsis passing along the greater and lesser curvatures. There was no constant stiffening in any one part. In Case 1 peristalsis was diminished over the involved area. All 3 showed the greater curvature to be involved. In studying these cases over a period of time serial variations occurred which corresponded closely to the clinical condition of the patient. The diagnosis of the condition is important from the viewpoint of treatment, as subtotal gastrectomy is the most satisfactory procedure if the extent of involvement and the patient's condition permit of its being done. It has been carried out successfully in 2 cases reported by Strauss, Meyer and Bloom.

**Case Reports.** CASE 1.—November 28, 1928 (Fig. 2). R. L. M., aged 49 years, weighed 145 pounds (maximum) and 121 pounds (present), chemist, had had no serious illness in childhood and none in adult life except pneumonia 20 years ago, with good recovery, and hemorrhoids, with successful operative treatment, before he was accepted for overseas service, June, 1917.

He went to France with the infantry, March, 1918, and was in the operations about Amiens. In June, 1918, he reported to his medical officer, complaining of loss of appetite, "water brash" and constipation, and this continued more or less until August, when he developed pyrexia of unknown origin, and was sent to the Casualty Clearing Station, August 27, to Le Treport, August 30, and then to Bassingstoke for 3 or 4 months. He was suffering from serious obscure digestive trouble—epigastric pains, nausea, vomiting, some belching and pain usually about an hour after food. From 1920 to 1927 he was employed in a drugstore and occasionally was off for a week or two complaining of epigastric pains; he felt exhausted, nervous, irritable, apprehensive and suffered from frontal, occipital and temporal headaches; "felt floored and done up." His digestive trouble grew worse—epigastric pains, flatulency, constipation, nausea and vomiting immediately after eating or drinking. He finally gave up work, October 23, 1927, and was under the care of J. G. Lee, who diagnosed duodenal ulcer. Radiologic examination (Tovell) showed evidence of gastric polyposis, the duodenum

not being visualized. He became reduced in weight to 93 pounds. In January, 1928, he began to improve, but had a recurrence of obstructive symptoms, with nausea and vomiting in March, 1928, and was put back on Sippy diet.

He is small, thin, of nervous type; color good; has improved in health sufficiently to undertake part-time work. He has no nausea or vomiting at present but "water brash;" epigastric discomfort usually when the stomach is empty; feels bloated after meals; bowels constipated; on abdominal examination no tumor is felt, but some tenderness and sense of increased resistance over epigastrium; physical examination otherwise of no special importance. Blood pressure, 90 systolic and 60 diastolic.

During the winter of 1929 he had recurrent attacks of "water brash," persistent epigastric soreness, bloating and occasional vomiting after meals; stools dark at times apart from taking medicine; sensitiveness and increased resistance over epigastric area.

*Examination of Stomach Contents After Ewald Breakfast.* December 15, 1928: 200 cc. of sour material; free acid, 60; total acid, 100; occult blood (bezidin), negative. March 21, 1929: Free acid, 80; total acid, 100; occult blood (bezidin), negative.

*Examination of the Blood.* Hemoglobin, 95 per cent. The red blood cells were of good size and shape and there is no leukocytosis. A differential count of the stained smear showed the following percentages of white blood cells: Polymorphonuclears, 45; lymphocytes, 39; transitionals, 9; eosinophils, 3; large mononuclears, 3; basophils, 2.

The Wassermann reaction was negative.

The urinalysis gave normal findings.

*Gastrointestinal Radiologic Report.* October 26, 1927 (Tovell): *Screen.* The meal passed through the esophagus without any evidence of obstruction. The stomach filled. Peristaltic waves were present and passed to the pylorus. The greater curvature was extremely rough and irregular in outline, but under manipulation could be indented. The stomach was freely movable.

*Plates.* The plates show evidence of marked roughening and irregularity involving the whole of the greater curvature extending from the cardiac end almost to the pylorus. The lesser curvature does not show any extensive change. There appears to be evidence of peristalsis noted on the greater curvature. There is no persistent deformity such as one would expect to find if carcinoma were present. The first portion of the duodenum seems to be fairly well filled on one of the plates.

*Six Hours Screen.* The stomach was empty. The meal occupied the cecum and terminal ileum. Both were independently movable. There was no obstruction to the small bowel.

*Conclusions.* From the examination there is evidence of marked deformity involving the stomach, particularly the greater curvature, suggestive of polyposis. There is no evidence of growth involving the colon.

In all, 7 radiologic examinations have been made at varying intervals, and while the gastric indentations varied from time to time, in general the deformities were the same.

In this case the presence of hyperchlorhydria and the absence of egg-white mucus in the gastric contents is against the diagnosis of polyposis. The question arises whether the radiologic findings are sufficient to warrant the diagnosis.

January 30, 1931: This patient has been under observation 3 years and 5 months since the first radiologic examination, and continues in fairly good health.

CASE 2.—May 10, 1928 (Fig. 3). Mrs. H. W., aged 54 years, 5 feet 6 inches in height, weighed 155 pounds (maximum) and 118 pounds (present). Family history: Her maternal grandfather probably had myxedema her mother died of myxedema at 45 years, two sisters developed myxedema after childbirth and her only son's appearance suggests Fröhlich's syndrome. She is ordinarily vigorous and active. She had inflammatory rheumatism at 16 years; recovered, but had a recurrence after coming to Toronto, in 1902. She had four attacks of hematemesis, the first as a girl, the last some 20 years ago, after her husband's sudden death. She has suffered more or less for years from rheumatic manifestations, especially in the fingers, shoulders, back and hips. The bowels are constipated and there has been more or less indefinite digestive disturbance for years. She has three devitalized teeth and fairly marked chronic tonsillar infection; some chronic bronchitis, scattered, sibilant and moist râles; slight cough and thick greenish-yellow morning expectorations. No tubercle bacilli were found in the sputum. Temperature was normal. The blood pressure was 100 systolic and 66 diastolic. The heart was normal. The abdomen was scaphoid, with marked gastric succussion splash to below the navel; there was "squashiness" over the cecum and some sensitiveness below and to left of the navel. The patient is definitely hypothyroid and is taking thyroid extract.

Laboratory examinations included: Negative urinalysis.

The Wassermann reaction was negative.

The blood count showed: Hemoglobin, 90 to 95 per cent; red blood cells, 4,800,000; color index, 0.9; white blood cells, 9000. The red blood cells are of good size and shape and a differential count of the stained smear shows the following percentages: Polymorphonuclears, 51; lymphocytes, 46; eosinophils, 2; basophils, 1.

*Radiologic examination* showed evidences of an old duodenal ulcer without gastric stasis. There is marked irregularity of the greater curvature both on screen and plates, suggestive of polyposis.

October 4, 1928: After clearing up oral infection, tonsillar enucleation and 2 months' holiday the patient was much better and had gained 7 pounds in weight.

The question arises again in this case as to the interpretation of the radiologic plates. Does the irregularity of the greater curvature warrant the diagnosis of polyposis and recourse to operation? Further clinical and radiologic study, checked by surgical and autopsy experience of such cases, is evidently required, and in the meantime the procedure adopted should be determined by clinical developments. After nearly 3 years this patient's condition has materially improved.

CASE 3.—January 25, 1929: Mrs. G. B., aged 37 years, weighed 135 pounds (maximum) and 94 pounds (present). Ordinarily active and vigorous, of nervous temperament, she has had no serious illness except albuminuria with her last pregnancy, 14 years ago. During the past 18 years she has suffered from belching of gas; severe epigastric pain at times, not related to time of eating or character of food; no nausea or vomiting; bowels regular and free; moderate pyorrhea about the remaining nineteen teeth; moderate chronic tonsillar infection; occasional sore throat. In recent years she has suffered from lumbago and sciatica. Heart and lungs showed nothing abnormal on physical examination. Blood pressure, 100 systolic and 74 diastolic. In the abdomen there was well-marked



epigastric "squashiness;" no definite tenderness but a sense of increased resistance toward pylorus.

Laboratory findings included:

Negative urinalysis.

The Wassermann reaction was negative.

The blood count showed fairly marked secondary anemia; hemoglobin, 80 per cent; red blood cells, 4,800,000; white blood cells, 9000. Differential count percentages showed: Polymorphonuclears, 61; lymphocytes, 36; Eosinophils, 2; transitionals, 1.

*Radiologic Examination.* January 26, 1929 (Tovell): The stomach filled. Peristaltic waves were present and passed to the pylorus both on the greater and lesser curvature. The greater curvature showed slight irregularities in the dependent portion extending to the pylorus. These irregularities were more accentuated in the prone position. On inspiration the greater curvature passed downward, filling fairly well, except for several serrated deformities near the pylorus. No palpable mass was elicited. The duodenum was normal.

*Plate.* The plate confirms the observations made on the screen and showed the same irregularities, which are not due to spinal pressure. In the lateral position they are quite distinct.

*Six Hours Screen.* About  $1\frac{1}{2}$  ounces remained in the stomach at the end of 6 hours.

April 3, 1929: Reëxamination showed evidence of the irregularities formerly described.

*Plates.* The plates confirm the observations on the screen and show the irregularities to be outside the region of spinal pressure and not so pronounced as on the first examination. There was no evidence of retention.

There is no radiographic evidence of ulceration or malignancy involving the stomach or duodenum. The defects noted on the screen and plates are strongly suggestive of polyposis. The changes are mostly on the greater curvature in the pyloric region.

In the 2 years since this patient came under observation her condition has improved.

April 8, 1929 (Fig. 4). The patient's condition is much improved after removal of infected teeth; she has gained 6 pounds in weight; rheumatic pains have disappeared; anemia is less marked; digestion much better; tonsils are definitely infected.

Blood findings were as on the previous examination, except for a slightly increased hemoglobin content.

Stomach contents after Ewald test breakfast: Free acid, 22; total acid, 41; occult blood (benzidin), negative.

In this case there was absence of egg-white mucus in the stomach contents, and free hydrochloric acid and total acidity were normal. While the radiologic findings are suggestive, one does not feel that, with our present knowledge, they are sufficiently conclusive to warrant an assured diagnosis of polyposis and surgical treatment.

A specimen in the University of Toronto Pathologic Museum of marked thickening of the gastric and intestinal mucosa, was obtained from a soldier, aged 68 years, who has been ill for over 2 years with ecchymoses about the eyes, forearms and chest; diarrhea with blood, abdominal pain and distention, weakness and anemia. The blood showed a typical condition of a chronic splenomyelogenous leukemia. The interglandular structure of the stomach and intestine was found infiltrated by myelocytes; there

was general lymph node enlargement. The specimen is interesting from the fact that the gross appearance is very similar to that of *polyadenoma en nappe*. A gastrointestinal radiologic examination was not made, and one can only speculate as to whether this would not have been a case in which the radiologic findings would be difficult to differentiate from diffuse polyposis.

Another specimen (Fig. 7) in the University of Toronto Pathologic Museum presents the gross appearance of *polyadenoma en nappe*, with an ulcerated area of malignant degeneration in its center. It was obtained from a patient, E. L., aged 50 years, male, who had suffered from abdominal discomfort for some months before consulting his physician in August, 1923. At this time a radiologic examination suggested a large benign ulcer of the lesser curvature of the stomach. At operation the condition was thought to be carcinoma and a gastroenterostomy was done. Radiologic examination 3 months after operation was negative. The patient continued very well until March, 1924, when gastric symptoms recurred. A radiologic examination at this time again suggested gastric ulcer. At operation a gastric carcinoma was found, but too extensive for removal. The patient died, April 24, 1924, and at autopsy the whole mucous membrane except the pyloric antrum was thrown into large irregular folds or polypoid masses resembling the convolutions of the brain. Sections from the central ulcerated area showed a carcinomatous structure—columns and groups of atypical epithelial cells supported by delicate stroma.

The gross appearance of the specimen suggests *polyadenoma en nappe*, with secondary carcinomatous transformation. In view of the condition found at autopsy, it is difficult to understand the radiologic findings. It is scarcely possible that the diffuse polypoid condition developed subsequent to the radiologic examination some 6 weeks previous to death. If it existed before that time and was not revealed by the examination, then radiologic diagnosis cannot always be depended upon to demonstrate the condition, and negative radiologic findings do not necessarily exclude the possibility of polyposis.

**Summary.** 1. The literature on polypi and polypoid conditions of the gastrointestinal tract is reviewed, and their etiology, symptomatology, radiology, pathology and relationship to carcinoma discussed.

2. Three cases of gastrointestinal disease with peculiar radiographic findings suggestive of polyposis are reported, and their progress over a period of two years or more reported. The question as to whether a diagnosis of polyposis is warranted on the radiologic findings is discussed and also the advisability of surgical treatment.

3. An unusual case of polypoid tumor of the duodenum is described.

4. A specimen of leukemic hyperplasia of the gastric mucosa is

presented with gross appearance suggestive of that of *polyadenoma en nappe*.

5. A specimen of *polyadenoma en nappe* with cancerous transformation is described.

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## BRITTAİN'S PATHOGNOMONIC SIGN OF GANGRENOUS APPENDICITIS.

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In many patients in whom the diagnosis of appendicitis was not made before operation the disease has been found to exist when the abdomen was opened. On the other hand, there have been many

cases in which, though everyone was quite positive of the diagnosis of appendicitis before operation, the appendix was found to be either normal, trivially, chronically or pre-pathologically diseased.

Most surgeons of experience are quite willing to admit that in many cases there are numerous errors in predicting the exact type of lesion to be found in a given case at a given moment. For this reason experienced doctors are prone to urge, on the one hand, immediate operation in every case and, on the other hand, a reasonable delay for longer observation. The practical effect is that we have often found the appendix to be gangrenous when that was unsuspected, and we have often found the appendix to be normal or slightly diseased in cases in whom it was deemed wise to perform an emergency operation upon first sight.

In July, 1928, Dr. R. Brittain, an intern in the Richmond Memorial Hospital, was examining with me a young man in whom there was no doubt that he needed prompt operation for appendicitis. Upon palpation of the abdominal wall there was noted, in addition to tenderness and spastic rigidity of the overlying muscles, that the right testicle was suddenly retracted to the upper part of the scrotum. Repeated examination showed that this invariably occurred whenever the lower right quadrant was palpated, and the testicle remained retracted as long as the pressure was made. Upon relief of pressure, the testicle immediately dropped to its original position.

Operation revealed that the appendix was gangrenous, the peritoneum fiery red and the cavity contained amber-colored exudate in this region.

We had never observed this phenomenon before, and upon questioning a great many doctors and surgeons in the community we could find no one who had made the observation.

From this time we began to look for the sign in every case of appendicitis and of other conditions bearing resemblance in symptomology to this disease. We have now observed it in nearly 500 cases of gangrenous appendicitis and have failed to observe it in more than 300 other acute abdominal affections, such as intestinal obstruction, gall bladder and ulcer diseases, kidney and ureteral colic, and nonsurgical affections, such as functional colicky pains, following dietetic indiscretions and the taking of purgative medicines.

For more than 2 years now, since the observation of the first 100 cases, we have come to look upon the sign as pathognomonic of gangrenous appendicitis, and proceed to operate upon the patient without further delay. On the other hand, when the sign is absent we have felt quite sure, and this has been substantiated by operation, that the disease, if appendicitis at all, is not gangrenous, and do not hesitate to defer operation for further study.

During our observations, before we had had sufficient experience to feel justified in acting upon our tentative conclusion of the

value of this sign, we operated upon a few patients in whom we believed appendicitis to exist, and in whom we found the appendix was normal. One striking case of this was the case of a little boy, who had abdominal pain for 48 hours, together with vomiting, tenderness, and even the indication of a small mass which we thought was a small appendiceal abscess. He did not have Brittain's sign, and before operation we announced that we might have been pinning too much faith upon the sign. Operation revealed that the boy had intussusception of the small bowel, with complete mechanical obstruction, and a normal appendix.

There have been a few other errors of observation and interpretation of the sign. In one of the earlier cases, in a man nearly 70 years of age, the retraction was so slight that we were not sure it existed. We found at operation next morning a gangrenous appendix. In many cases, however, since this one, we have noted the sign in patients as old as 65 years, and just recently in a man aged 76 years; though one can easily imagine the retraction in such cases could rarely be so active as in younger men.

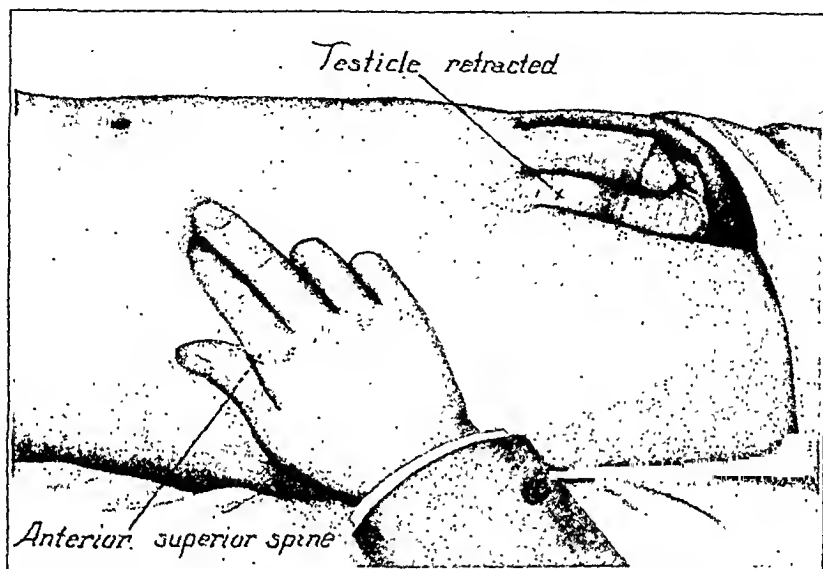
We made an important observation in one case in which by pressure exactly at the outer edge of the right rectus muscle exactly at the line of the umbilicus the right testicle retracted conspicuously. This was not interpreted as Brittain's sign. There was no retraction, no rigidity and no tenderness upon pressure in the right lower quadrant. There was some question of gall bladder disease. Roentgen ray showed bone changes in the spine, possibly a product of arthritis. Exploratory operation showed nothing abnormal in the abdomen. Could the tenderness and testicle retraction elicited by pressure exactly at the site of entrance of a nerve into the rectus muscle have been the result of neuritis incident to spinal arthritis?

In young children the testicles retract so easily that it is easy to be deceived in believing the sign is present when it is not. We have noted, however, that normal retraction influences both testicles (is not confined to the right side), and this is of differential diagnostic value.

In widespread peritonitis secondary to perforating ulcer of 24 hours or longer duration the testicle may be pulled up into an abnormally high position independently of pressure, and retained, *i.e.*, it does not come higher when pressure is made and does not go down when the palpating hand is removed. We note, therefore, that the sign of appendicitis involves both phenomena, namely, retraction upward when a palpating hand is applied, and return downward when pressure is removed. The sign is not influenced by morphin.

A certain technique in making the examination is necessary. The patient should be quietly at rest, the bedclothes pulled well down, a careful inspection made before the examining hand is applied and the patient's mind diverted from the test. Careful

palpation of the left side and upper abdomen is made before the right lower quadrant is touched. Then, upon a gentle touch of the lower right quadrant, especially at the McBurney area, as soon as the finger is applied the testicle is seen to retract upward. As long as the finger is held in contact the testicle remains in this position. As soon as it is removed the testicle will drop back to its original position.



Showing the retraction of the testicle when pressure is made on McBurney's point, in a case of gangrenous appendicitis. The testicle is normally located in the area surrounded by the dotted line.

It has been observed in some cases that, with the hand remaining gently on the abdominal wall, the testicle may drop back to its original position and then upon the removal of the finger will again retract (rebound retraction).

We thought for a while that in cases of gangrenous appendicitis located high up behind the cecum the sign might not appear or be less active. Further observation showed that it was present even in these cases, though it was less noticeable when pressure was made at McBurney's point than when pressure was made slightly higher toward the loin.

Now, with ample experience in the differential diagnosis between appendicitis and the other diseases with which we have so often found difficulty and made errors, we feel it desirable to present this sign to the profession, and have named it in honor of the young man who first noticed it, Brittain's sign.

The explanation of this phenomenon will still have to be theoretical. We assume that it is a manifestation of muscular contrac-

tion involving the internal oblique and its cremaster portion, which surrounds the spermatic cord and draws the testicle up. This is commonly explained upon the same basis as is the contraction of the right rectus muscle and the external oblique, by the transmission of the impulse from the point of irritation (the appendix and peritoneum) to the spinal cord and back over the motor nerves of the reflex arc to the muscles of the abdominal wall and the spermatic cord.

**Summary.** In the presence of gangrenous appendicitis palpation of the lower right quadrant of the abdomen invariably produces sudden retraction of the right testicle, which drops to its original position as soon as pressure is withdrawn.

The constant presence of this sign, first observed by Dr. Brittain, in 1928, in nearly 500 cases of gangrenous appendicitis, and its absence in more than 300 other acute abdominal conditions, make it, we believe, pathognomonic for gangrenous appendicitis.

## STUDIES IN COMPLETE HEART BLOCK.

### I. THE CARDIAC OUTPUT AND THE PERIPHERAL CIRCULATORY MECHANISM.

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ALTHOUGH numerous clinical and electrocardiographic studies of complete auriculoventricular block have been published, less attention has been given to the physiologic changes in the hemodynamics of this condition. In recent years it has become increasingly recognized that abnormal functioning of the heart is frequently accompanied by changes in the peripheral circulatory mechanism. In spite of the fact that the methods available for studying the physiology of the circulation in man are often indirect and limited in applicability, significant results may be obtained when several procedures are carried out simultaneously in a series of cases.

Complete heart block is a clinical condition of not infrequent occurrence which is generally considered of serious prognostic significance but which may exist for many years without symptoms. In order to maintain normal bodily functions in this condition, in



the presence of the striking changes in the cardiac mechanism, it is probable that compensatory adjustments occur throughout the entire vascular system. These readjustments may be in the nature of an increase in the stroke output of the heart or of changes in the blood pressure, blood volume, oxygen transport by the blood or possibly in the peripheral vascular tone. The aim of this study was to determine the nature and extent of these circulatory adjustments.

**Clinical Protocols.** Studies were made on 5 patients with complete heart block who varied in age, extent of incapacity and objective signs of cardiac failure. As the clinical protocols are of importance in interpreting the observations, they are presented before the experimental data.

**Case Reports.** CASE I.—L. S., aged thirty-three years, male, Jewish, newspaper reporter. As a child he had a throat infection which may have been diphtheria, but had never had syphilis or any rheumatic infection. For about ten years he had suffered from intermittent attacks of epigastric pain accompanied by considerable gas. Peptic ulcer was suspected, but it was considered more probable that his symptoms were due to gastric neurosis. Seven years ago a complete heart block was discovered during the course of a routine physical examination, which persisted to date. There had never been any cardiac symptoms in spite of the fact that the patient was very active physically—a long-distance swimmer and a gymnast.

The physical examination was essentially negative. There was no pulsation in the neck. The heart was not enlarged to percussion; the sounds were regular at a rate of 40 per minute and of good quality, although there was some variation in the intensity of the first sound. No murmurs were heard. There was no arteriosclerosis or edema. The systolic blood pressure was 128 and the diastolic 80. The lungs were normal. The Wassermann reaction of the blood was negative. A teleroentgenogram of the heart showed it to be normal in size and shape; under the fluoroscope the ventricular contraction appeared forcible, the contraction of the heart being about 1 cm. with each beat. Measurements of the heart shadow were 8.2 cm. to the right and 4.7 cm. to the left, giving a total transverse diameter of 12.9 cm. The internal diameter of the chest was 28.1 cm. Repeated electrocardiograms always showed complete heart block with an auricular rate of 60 and a ventricular rate of 40; the *P-P* intervals being slightly shorter when a ventricular complex fell between them. The *Q-R-S* complexes were normal and the *T* waves upright in all leads. The axis was normal.

**Diagnosis.** Complete heart block. Etiology questionable, possibly of congenital or diphtheritic origin. Gastric neurosis.

CASE II.—R. S., aged thirty-three years, colored housewife, in perfect health. She had never had diphtheria, syphilis or any rheumatic infection. Her slow heart rate was first noted nine years ago, during the course of a routine insurance examination and probably had persisted since. She had never had any cardiac symptoms, although she led an active life.

Physical examination was essentially negative. There was no pulsation in the neck. The left border of the heart was percussed 10 cm. to the left in the fifth costal interspace, 2 cm. outside the midclavicular line. The sounds were of good quality, regular, at a rate of 35 per minute. There was a variation in the character of the first sound both at the apex and base; sometimes it was loud and snapping, and at other times muffled. No murmurs were heard. The lungs were clear; there was no arteriosclerosis

or edema. The blood pressure was 115 systolic and 70 diastolic. The Wassermann reaction of the blood was negative. Teleroentgenogram measurements of the heart showed slight transverse enlargement. The heart show measured 8.9 cm. to the left and 4.9 cm. to the right, giving a total transverse diameter of 13.8 cm. The internal diameter of the chest was 24.1 cm. Fluoroscopic examination showed an increased ventricular excursion, the ventricle contracting 1 to 1.5 cm. with each beat. The electrocardiogram showed complete heart block, with an auricular rate of 75 and a ventricular rate of 35 per minute. The *Q-R-S* complexes were normal and the *T* waves upright in the first and second leads, but inverted in Lead III. There was left ventricular preponderance.

*Diagnosis.* Complete heart block of doubtful etiology, possibly congenital.

CASE III.—O. L., aged seventy-eight years, Norwegian, janitor; entered the hospital with a complaint of dizziness and fainting. His past history was unimportant; he had never had diphtheria, syphilis or any rheumatic infection. One month before entry he began to be moderately dyspneic on exertion. Two weeks later he developed a dull pain beneath the left clavicle which came and went without relation to exertion. One week before entry he experienced a sudden transient attack of faintness and dizziness. Similar attacks recurred about twice daily until he entered the hospital. At that time he also noted slight orthopnea and edema of the ankles. Physical examination on entry showed a rather thin old man in no distress. There was a marked arcus senilis and moderate sclerosis of the fundal vessels of the eye. The heart borders could not be accurately determined. The sounds were regular at a rate of 38 and of fair quality. There were no murmurs. The aortic second sound was accentuated. There was moderate peripheral arteriosclerosis and slight edema of the ankles. The systolic blood pressure was 270 and the diastolic 80. The lungs were emphysematous, but otherwise negative. The Kahn reaction of the blood was negative. The urine showed a specific gravity of 1.015 to 1.020, and on repeated examination albumin ranged from none to a trace. There were occasional hyalin and granular casts.

The heart showed moderate transverse enlargement by roentgenogram, with a prominent left ventricle. The aorta was tortuous and calcified. Electrocardiogram showed complete heart block with an auricular rate of 90 and a ventricular rate of 40. The *Q-R-S* complexes were normal; the *T* waves were diphasic in the first lead and upright in the other two. The axis was normal. The patient was digitalized and kept in bed; he improved slightly, and the edema disappeared. His condition became stationary; he was quite comfortable in bed, but on exertion dyspnea and dizziness returned. Six weeks after entry the special clinical studies were made. A month later he had three marked Adams-Stokes attacks in one week. Four months after entry his dyspnea became somewhat worse; a month later he developed bronchopneumonia and died. Autopsy was not obtained.

*Diagnosis.* Complete heart block, etiology arteriosclerosis; arteriosclerotic heart disease.

CASE IV.—M. G., aged fifty-eight years, American housewife, was admitted because of fainting spells. Her past history was unimportant; she had never had diphtheria, syphilis or any rheumatic infection. Two years before entry she began to be dyspneic on exertion, to tire easily and to have slight edema of the ankles. Her local physician told her she had high blood pressure and diabetes, and he limited her activity and her diet. Shortly after this she had her first fainting attack and subsequently had about twenty up to the time of entry to the hospital. All of her symptoms gradually increased in intensity.

Physical examination on entry showed a rather obese woman comfortable in bed. There was slight arteriosclerosis of the vessels of the eyegrounds. A venous pulsation at a rate of 90 was seen in the neck. The lungs were clear. The heart was enlarged, the left border being percussed 14.5 cm. in the fifth intercostal space. The sounds were of fair quality and regular at a rate of 30. There was a harsh systolic murmur, best heard in the second and third interspaces, transmitted to the neck with a systolic thrill. The aortic second sound was accentuated. The liver was palpated 4 cm. below the costal margin. There was slight edema of the ankles. The blood pressure was 240 systolic and 70 diastolic. The Kahn reaction of the blood was negative. The urine was negative except for a trace of sugar on entry; this disappeared under treatment.

Teleroentgenogram showed that the shape of the heart was consistent with a mitral deformity in the region of the left auricle and enlargement to the left. The measurements of the heart shadow were 13.4 cm. to the left and 5.2 cm. to the right. The total transverse diameter was 18.6 cm.; the internal diameter of the chest, 27 cm. The first electrocardiogram showed complete block, with an auricular rate of 90 and a ventricular rate of 30. The *Q-R-S* complexes were prolonged to 0.12 to 0.14 seconds and were slurred in all leads. The *T* waves were opposite the main deflection of the *Q-R-S* complex in each lead. The findings were typical of left bundle-branch block. A few days later another electrocardiogram resembled the preceding except that right bundle-branch block now existed. A possible explanation for the development of first left and then right bundle-branch block in successive electrocardiograms is that the origin of the impulse which excited the ventricular contraction was first in one branch of the bundle of His and subsequently shifted to the other branch.

With rest in bed the patient improved considerably. The edema cleared up, the liver diminished in size and she had no Adams-Stokes attacks during the six weeks she remained in the hospital. The studies reported here were performed about two weeks after entry. Her symptoms, however, soon recurred. She reentered the hospital a month later, had repeated Adams-Stokes seizures of great severity, some relieved only by adrenalin, and finally died in such an attack. Autopsy was not obtained.

*Diagnosis.* Complete heart block, etiology arteriosclerosis; arteriosclerotic heart disease; aortic stenosis; bundle-branch block; diabetes mellitus.

**CASE V.**—M. T., aged fifty-seven years, American housewife, who was admitted with a complaint of shortness of breath. She gave no history of diphtheria or syphilis and had been well until four years before entry, when she had an attack of a migratory polyarthritis with fever. Shortly afterwards she had several fainting spells and was under treatment for several weeks for heart trouble in this hospital. At this time an electrocardiogram showed partial heart block with a *P-R* interval of 0.28 seconds and a rate of 57. The patient then improved and felt fairly well until a year and a half before entry. After that time she had increasing edema and dyspnea on exertion and for several weeks was bed-ridden.

Physical examination on entry showed a dyspneic, cyanotic woman. The veins of the neck were somewhat congested. The lungs showed moderate dullness and râles at each base. The heart was greatly enlarged to the left. The sounds were regular and of rather poor quality at a rate of 36. Blowing systolic and middiastolic murmurs were heard at the apex, and a blowing diastolic murmur along the sternal border. No peripheral arteriosclerosis was noted. There were marked ascites and extensive anasarca. The systolic blood pressure was 210 and the diastolic 80.

The Kahn test of the blood was negative. Teleroentgenogram of the heart showed marked transverse enlargement and widening of the great vessels. An electrocardiogram showed complete heart block with a ven-

tricular rate of 37. No *P* waves were visible. The *Q-R-S* complexes measured 0.08 to 0.12 seconds and were slurred, probably due to intraventricular block. The *T* waves were flat in Lead I and inverted in Leads II and III. The axis was normal. With rest in bed the patient improved but slightly, and her condition then became stationary. The special studies were carried out ten weeks after admission, when her physical condition was but little better than it was on entry. She was discharged a few weeks later. While at home her symptoms persisted, gradually grew worse, and she died nine months later. No autopsy was obtained.

*Diagnosis.* Complete heart block, etiology rheumatic fever; rheumatic heart disease; mitral stenosis and regurgitation; aortic regurgitation; probably auricular fibrillation; intraventricular block; marked congestive heart failure.

*Methods of Observation.* The blood pressure was determined by a mereury sphygmomanometer; the vital capacity by a Collins spirometer. The circulation time was found by the histamin reaction method.<sup>1</sup> The cardiac output was estimated according to the technique of Field, Bock, Gildea and Lathrop.<sup>2</sup> The principle of this method is that first described by Fick whereby the carbon dioxid contents of the arterial and mixed venous bloods in the lungs are indirectly estimated from an analysis of respiratory gas samples. The heart output is then calculated by dividing the carbon dioxid excreted by the subject per minute by the difference between the arterial and mixed venous carbon dioxid contents. Seven alveolar and "virtual venous" gas samples were obtained for each determination. In one instance the acetylene method of Grollman<sup>3</sup> was also employed. The blood volume was calculated by the dye method.<sup>4</sup> The venous pressure was measured by the direct method of Moritz and Tabora,<sup>5</sup> except that the Eyster indirect technique<sup>6</sup> was employed with Case V. In our experience the results obtained by these two methods are comparable.

The metabolism of the first 4 patients was obtained by the Tissot method and of the fifth patient by a Collins spirometer. For the determination of the oxygen and carbon dioxid content of the blood samples were taken under oil from the cubital and femoral veins without stasis and from the femoral artery. The analyses were carried out according to the manometric method of Van Slyke.<sup>7</sup> Lactic acid determinations were made according to the technique of Friedemann, Cottonio and Shaffer.<sup>8</sup> All studies were made in the postabsorptive state in semirecumbent position.

*Interpretation of Results.* Tables I, II and III outline the results of these observations and give the averages and ranges for similar determinations obtained by us at various times on groups of normal individuals. Our normal figures agree closely with the findings of other investigators who used the same techniques.

The 5 patients studied showed clearly three grades of circulatory functional capacity. Cases I and II had no functional impairment whatever. Cases III and IV were compensated at rest at the time

TABLE I.—MEASUREMENTS OF THE ARTERIAL AND VENOUS BLOOD PRESSURES, THE RESPIRATORY EXCHANGE, THE RATE AND VELOCITY OF THE CIRCULATION, THE BASAL METABOLISM, THE BLOOD VOLUME AND HEMATOCRIT, AND THE VITAL CAPACITY.

Case.	Heart rate per min.		Arterial blood pressure, mm. Hg.		Venous pressure, mm. Hg.		Respiratory minute volume output, l.		Carbon dioxide tension, mm. Hg.			Carbon dioxide output per minute, cc.		Cardiac output per minute, l.		Cardiac output per 100 cc. O <sub>2</sub> consumption, l.		Cardiac output per beat, cc.		Basal metabolism.		Circulation rate, sec.		Blood volume.		Hematocrit, per cent.		Vital capacity, cc./sq. m.	
	Systolic.	Diastolic.							Alveolar.	Virtual venous.	Difference.	per minute, cc.	minute, l.	100 cc. O <sub>2</sub> consumption, l.	per beat, cc.	Per cent.	Cal./hr./sq. m.	Per cent.	Cal./hr./sq. m.	Cc.	Cc./sq.m.	23 to 30	3278* 2730 to 4040*	41* 36 to 47*	2500				
I (L. S.) . . .	106	70	+	4	7.2	42.7	50.2	7.5	157	5.09	2.8	139	-20	31.5	24	4025	2470	46	2800										
II (R. S.) . . .	115	70	+	2	6.4	40.1	47.3	7.2	145	4.92	2.8	123	-22	30.6	29	3425	2100	41	1530										
III (O. L.) . . .	270	80	+	3	6.2	36.5	43.2	6.7	151	5.28	2.9	147	-12	31.9	...	3865	2350	35	1400										
IV (M. G.) . . .	240	70	0		8.4	32.5	39.6	7.1	154	4.60	2.3	141	-4	34.1	47	3620	2430	42	1540										
V (M. T.) . . .	210	80	+14		5.7	37.4	44.3	6.9	139	4.69	2.6	156	-1	34.7															
Normal average . . .	..	..	..	..	6.9	39.8	47.8	7.6	202	6.7	2.7	101	...	..	23	..	3278*	41*	2500										
Normal range . . .	..	..	+10		..	..	..	..	..	..	..	..	-15 to +15	..	15 to 30	..	2730 to 4040*	36 to 47*											

\* Normal figures as given by Rowntree, Brown and Roth.<sup>4</sup>

of the investigation, but showed definite evidence of myocardial damage and developed symptoms on slight exertion. (Class 2b of the American Heart Association Classification.<sup>10</sup>) Case V remained decompensated even in bed. (Class 3.) By evaluating the observation on all 5 patients, therefore, it should be possible to show not only what physiologic changes the heart block in itself produces in the circulatory mechanism, but also what further changes may take place as the myocardial reserve is progressively diminished.

TABLE II.—THE CARDIAC OUTPUT IN CASE II AS MEASURED BY THE ACETYLENE METHOD.

Case.	Heart rate per min.	Arterio-venous O <sub>2</sub> difference, cc./L.	Oxygen consumption per min., cc.	Cardiac output per min., L.	Cardiac output per beat, cc.	Basal metabolism, per cent.
II (R. S.) . . .	36	58.6	187	3.20	89	-9
	36	55.9	187	3.36	93	
Normal average* .	...	59.3	...	3.88	60	

\* Normal figures as given by Grollman.<sup>9</sup>

TABLE III.—MEASUREMENTS OF THE OXYGEN AND CARBON DIOXID ARTERIOVENOUS DIFFERENCES AND THE ARTERIAL SATURATION IN CASES I, IV AND V.

Case.	Arteriovenous difference.				Arterial.		
	Arm.		Leg.		Content, vol. %	Capacity, vol. %	Saturation, vol. %
	Oxygen, vol. %	Carbon dioxid, vol. %	Oxygen, vol. %	Carbon dioxid, vol. %			
I (L. S.) . . .	3.35	3.27	5.23	3.16	18.44	19.13	96
IV (M. G.) . . .	2.63	1.92	5.24	4.35	17.97	20.07	90
V (M. T.) . . .	9.32	7.86	10.95	7.27	17.74	19.85	89
Normal average (13 cases) . . .	3.61	4.95	3.30	5.31	...	19.40	93
Normal range . . .	1 to 5	1.7 to 8.3	1 to 8	1.6 to 9.4	...	17.3 to 21.88	89 to 96

No attempt will be made to analyze the symptoms and physical signs of these patients. Such an analysis will be made from a larger series and published later.

*Arterial Blood Pressure.* Three of the patients showed the characteristic greatly elevated systolic and normal or low diastolic pressures which have often been noted in association with heart block. The 2 patients who had a normal arterial blood pressure were relatively young and without functional impairment, or evidence of organic myocarditis or peripheral arteriosclerosis. Possibly these 2 patients had elastic arteries which by stretching and

contracting assisted in the forward movement of the blood. The young patients thus showed an ability to adjust their circulatory mechanism to the heart block more simply than the others and without imposing the added strain which the compensatory systolic hypertension exerts upon the cardiovascular apparatus.

In the 3 cases in which high blood pressure existed the increase was evident only in the systolic pressure. This type of hypertension, then, is the direct result of increased ventricular discharge and bears no relation to the peripheral resistance except insofar as the high pressure depends upon the elasticity of the arterial system. Such hypertension is occasionally seen in persons with senile arteriosclerosis without heart block, but is fundamentally different in its nature from primary or essential hypertension. In the latter condition the fault lies in an increased peripheral resistance without an increase of the stroke volume and cardiac output, as has been shown by the authors<sup>11</sup> and others.

It is obviously impossible, therefore, to estimate from the arterial pressure alone whether the cardiac output per beat or per minute is normal. On the one hand, the blood pressure may be normal, with a marked increase in ventricular discharge, as in the first 2 cases of this series; on the other hand, the arterial pressure may be markedly elevated, although the cardiac output is not increased, as in cases of essential hypertension.

*Venous Pressure.* The venous pressure was normal in the 4 patients who were compensated at rest. The fifth case had an elevated venous pressure and also showed evidence of marked peripheral venous congestion. It is evident, therefore, that heart block *per se* does not tend to increase the venous pressure above the normal limits.

*Vital Capacity.* The vital capacity of the first case was normal. The reason for the somewhat lowered vital capacity in the second case is not evident, since she showed no objective or subjective evidence of pulmonary disease or venous stasis. The diminished vital capacity in Cases III and IV is in accord with the usual findings in persons who show a lowered cardiac reserve of similar extent.

*Cardiac Output and Velocity of Blood Flow.* Several workers have concluded, as a result of clinical observations and assumptions, in particular by taking the high pulse pressure as an index of increased ventricular discharge, that the output per beat in heart block is greatly increased. Von Bergmann and Plesch,<sup>12</sup> in 1909, applying the Fick principle, computed the cardiac output per beat and per minute in 1 patient and found the stroke volume increased to 200 cc. Lundsgaard,<sup>13</sup> Liljestrand and Zander<sup>14</sup> and most recently Smith, Walker and Alt,<sup>15</sup> using the Field and Boek application of the Fick principle, estimated the cardiac minute volume to be essentially normal during rest, with a consequent increase in the output per beat. During exercise patients with total block differ in their

ability to increase the cardiac output normally.<sup>13,14,16</sup> It is evident that this ability depends to a certain extent upon whether or not the ventricular rate is increased by exertion, since of all the cases reported only those who responded to exercise by a considerable increase in ventricular rates showed a normal increase in cardiac output.

The cardiac outputs of Cases I to IV in our series were determined. The technical procedure could not be carried out on Case V because of the pulmonary congestion. The cardiac outputs per minute as estimated in the 4 cases fell within the normal range. (Tables I and II.) Although the total cardiac outputs per minute were somewhat below the normal average, the blood flows per 100 cc. of oxygen consumption agreed closely with the average normal figure. To maintain this normal minute volume output of the heart in the presence of a markedly lowered heart rate the systolic discharge per beat had to be increased to a considerable extent in these patients. Our findings, therefore, agree closely with those of other observers as to the increase in stroke volume output and the maintenance of an essentially normal minute volume output at rest. No direct estimations of the amount of increase in blood flow during exercise were made.

The circulation rate from arm to face was determined in Cases I, II and IV. Changes in the circulation rate and in the cardiac output usually run parallel. However, if the cross section of the vascular bed is increased, the circulation rate may be greatly diminished without change in the cardiac output. In Cases I and II the circulation rate was normal. In Case IV, in spite of a normal cardiac output, the circulation time was greatly prolonged. Since the circulating blood volume in this patient was not increased, it would seem that there was a relative increase in the proportion of blood in the lungs with an increase in the cross sectional extent of the pulmonary vascular bed. That this increased blood volume in the pulmonary circuit does not invalidate the procedure for the determination of the cardiac output is evident from the fact that her arterial blood saturation was normal (90 per cent) and her alveolar carbon dioxid tension was within normal limits.

*Peripheral Blood Flow.* To check our findings as to cardiac output further and to gain some idea of the tissue consumption of oxygen, the oxygen and carbon dioxid contents and the arteriovenous oxygen and carbon dioxid differences of blood drawn from the cubital and femoral veins were measured. Although changes in the arteriovenous oxygen and carbon dioxid differences do not necessarily run parallel to changes in the cardiac output or blood flow as a whole, nevertheless, in our experience, a rough parallelism does exist—since the vessels from which the blood is drawn drain skeletal musculature (in particular, the legs) which represents at least 30 per cent of the oxygen consuming tissues of the body. Normally there is considerable individual variation between the



arteriovenous oxygen and carbon dioxid differences, but such variations fall within a definite range. Arteriovenous differences markedly higher than this range, therefore, are a strong indication of a reduction in the total blood flow. Our findings tend to corroborate this theory. (Table III.) In Cases I and IV, in which normal cardiac outputs were determined by the Fick principle, the arteriovenous oxygen and carbon dioxid differences from both arm and leg fell well within the normal range. In Cases I to IV the difference in carbon dioxid tension between alveolar and virtual venous gas samples was within the normal range (Table I)—a further indication of normal tissue exchange of gases. In Case V, who clinically was decompensated at rest and on whom it was technically impossible to determine the cardiac output, the arteriovenous oxygen and carbon dioxid differences were found to be definitely higher than the normal range. This suggests that in this patient the blood flow was diminished. Such diminished cardiac output in the presence of circulatory failure is to be expected, as it was also found by the authors in a group of patients with rheumatic heart disease.<sup>17</sup>

No evidence of an increase in the blood flow through the legs of Case V was found in spite of the fact that there was marked edema of the lower extremities. This is contrary to the finding reported by Harrison and Pilcher<sup>18</sup> of a decreased oxygen utilization from the blood flowing through an edematous extremity.

*Lactic Acid and Arteriovenous Oxygen Difference at Rest and After Exercise.* To throw further light on the state of the peripheral circulation both at rest and following mild exercise, lactic acid and arteriovenous oxygen difference determinations were made on Case I (L. S.) at rest and at intervals after he had performed a mild exercise (climbing two flights of stairs at a slow rate). In Table IV these values are given with the corresponding normal ranges and normal averages from identical procedures on a series of 10 healthy persons. It will be seen that the changes in arteriovenous oxygen difference were similar to the normal in direction and degree both in the arm and leg. Following exercise the patient's heart rate rose momentarily to 70, remaining regular, but subsided within thirty seconds to the resting level of 40.

The lactic acid content of the blood is also given in Table IV and Chart I, where it is compared both with the normal findings and those obtained in 10 compensated patients with heart disease. It will be seen that following exercise the rise is somewhat less than in the average normal case, and markedly less than in cardiac patients.<sup>19</sup> Since this man was a trained athlete, this finding, which is in accord with the work of Dill, Talbott and Edwards<sup>20</sup> on the effect of training on the circulatory mechanism, indicates that even in the presence of heart block the peripheral circulatory responses may be normal.

*The Hemoglobin Content of the Blood.* As judged either by the hematocrit readings or the oxygen capacity, none of the patients showed evidence of an increase in the amount of circulating hemoglobin, that is, a polycythemia. (Table I.) Case III showed evidence of a moderate anemia, such as occasionally occurs with advanced arteriosclerosis.

TABLE IV:—ARTERIOVENOUS OXYGEN DIFFERENCE AND LACTIC ACID CONTENT OF BLOOD TAKEN AT REST AND AT INTERVALS FOLLOWING EXERCISE IN CASE I.

Case.	Arteriovenous oxygen difference, vol. per cent.				Lactic acid, mg.				
	Resting.	After exercise.			Resting.	After exercise.			
		30 sec.	10 min.	20 min.		30 sec.	10 min.	20 min.	40 min.
LEG: I (L. S.) Normal average Normal range	6.9 3.3 1 to 8	14.6 10.0 7 to 13	3.9 3.3 1.5 to 5	7.3 4.1 2.5 to 7.5	15.6 12.2 8.8 to 15.1	18.8 27.5 17.4 to 43.8	16.4 18.4 15.3 to 26.9	17.0 14.4 to 22.6	16.4 14.5 10.8 to 17.5
ARM: I (L. S.) Normal average Normal range	4.3 3.6 1 to 5	10.5 9.8 4 to 12	4.5 3.8 1 to 5	... ... ...	13.3 13.5 9.8 to 17.2	16.8 16.0 13.1 to 20.7	15.4 15.8 13 to 18		

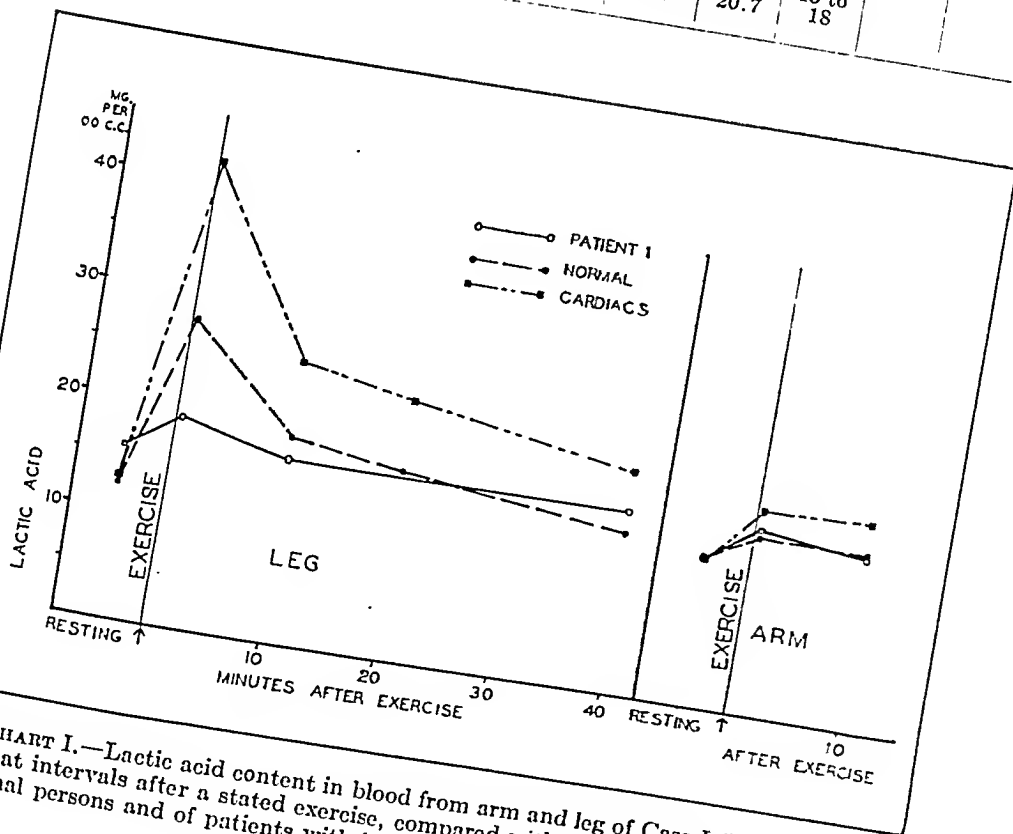


CHART I.—Lactic acid content in blood from arm and leg of Case I (L. S.), resting and at intervals after a stated exercise, compared with average values of a series of normal persons and of patients with heart disease.

*Blood Volume.* In each of the 4 patients in whom the blood volume was determined a reduction in the amount of circulating blood was found. (Table I.) Since this reduction in circulating blood volume existed without a decrease in the blood pressure or an increase in the minute volume flow, it is evident that there must have been a decrease in the extent of the peripheral vascular bed. In view of the fact that there was in no case any evidence of markedly increased peripheral resistance, it is most unlikely that the reduction took place to any extent in the arteriolar or capillary systems which are chiefly responsible for peripheral resistance.

*Basal Metabolic Rate.* In every case the basal metabolism was below the theoretical normal, although in only 1 case (Case I) did it fall below the lower limit of normal, namely,  $-15$ . (Table I.) It is not clear whether the organism readjusted itself to the altered circulatory conditions by decreasing its oxygen consumption or whether some underlying physiologic condition produced both complete block and a lowered metabolism.

*Discussion.* As a result of these observations on 5 cases of total heart block it is possible to summarize the circulatory changes which occurred in these patients. The blood flow was essentially normal at rest so long as the patient did not show evidence of circulatory failure in bed. To maintain a normal blood flow with a greatly reduced heart rate it is necessary for the output of the heart per beat to be increased markedly, and secondarily for the systolic arterial pressure to be raised, provided the peripheral vascular system is sclerosed and rigid. The circulating blood volume in the patients was somewhat reduced, and there was probably a diminution in the extent of the peripheral vascular bed. The peripheral resistance, however, was not increased. Whether our findings of a somewhat lowered basal metabolism has any relation to the heart block—either as cause or effect, it is impossible to state.

The symptoms of patients with heart block are of two types: (1) those of congestive or anginal heart failure, resulting from the myocardial degeneration which often accompanies the condition, and of which the heart block may be merely one manifestation; (2) the Adams-Stokes attacks, which are probably due to insufficient cerebral circulation brought about either by the inability of the heart to respond to the demands of exertion, by alterations in the peripheral circulatory adjustment, or, and this is probably the most common cause, by a local decrease in the irritability and responsiveness of the ventricles with periods of ventricular asystole. It is evident that complete heart block is not incompatible with a normal life and that the prognosis as to health and life is much more dependent on the presence or absence of accompanying myocardial disease than on the block itself.

*Summary and Conclusions.* 1. Studies were made on 5 patients with complete heart block, 2 of whom showed no, 2 moderate and 1 pronounced functional disability.

2. The 2 patients with no functional incapacity and no arteriosclerosis had normal arterial blood pressures. The remaining 3 had a systolic hypertension.

3. In the absence of cardiac failure the venous pressure was normal.

4. In the 4 patients with no circulatory failure at rest normal values for the cardiac outputs per minute were found. The cardiac outputs per beat in these patients were increased 40 to 50 per cent above the normal. In the fifth patient, with circulatory failure in bed, indirect evidence of a decreased blood flow was obtained.

5. The circulating blood volume was reduced in each of 4 patients. It was not measured in the fifth.

6. Four patients had basal metabolic rates in the lower part of the normal range; the fifth had a metabolism 20 per cent below normal.

7. The degree of elevation of the lactic acid and the changes of blood gases following exercise were normal in 1 patient who had good functional capacity.

8. The increased stroke volume of the heart, the systolic hypertension, the reduced blood volume and possibly the somewhat lowered basal metabolic rate may be considered compensatory responses tending to maintain a constant and adequate blood supply to the tissues during the prolonged diastolic pauses consequent upon the slow heart rate.

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## AORTIC ANEURYSM RUPTURING INTO THE CONUS ARTERIOSUS OF THE RIGHT VENTRICLE.

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IN a recent study of 100 aortic aneurysms coming to autopsy<sup>1</sup> it was noted that rupture occurred in 47 per cent of the cases. In the large majority of these the site of rupture was either into the pleural cavities or into some portion of the bronchial tree; rarely rupture occurred into one of the great vessels of the mediastinum, there being 2 cases in which an arteriovenous aneurysm was formed by perforation of the aneurysm into the superior vena cava. In 1 case the aneurysm had exerted sufficient pressure upon the pulmonary artery to cause some erosion of the vessel and to have been the immediate cause of death. In the case herewith reported rupture occurred into the conus arteriosus of the right ventricle. Antemortem diagnosis of the aneurysm was not made. The resulting physical signs were so typical of interventricular septal defect that the clinical diagnosis of *Maladie de Roger* was made, along with that of syphilitic aortitis and aortic insufficiency.

**Case Report. History.** H. C., a negro man, aged 28 years, laborer by occupation, was admitted to the John Sealy Hospital, October 2, 1929, complaining of shortness of breath and pain in the left chest. He dated his illness as beginning 3 months prior to entry, at which time he first noticed sharp and shooting pains about the heart and a feeling of fullness in the left chest. The pain was paroxysmal in nature, substernal in location and of short duration. About 2 months later he developed rather suddenly a severe moderately productive cough associated with severe dyspnea. Occasionally the sputum would be blood tinged. The dyspnea increased rapidly, and for the past week he was compelled to spend the entire night in a sitting posture in order to breathe. Night sweats had been experienced for about a week. There had been a loss in weight of 18 pounds.

The family history was irrelevant. With the exception of a penile sore at the age of 22 years, his past history was devoid of serious or significant illness.

**Physical Examination.** The patient was well developed, well nourished and showed marked respiratory distress. There was noticeable pulsation of the great vessels of the neck. Slight cyanosis was present. Many moist râles of the crepitant variety were heard over the bases of the lungs. The pulse was regular, rate 110 and Corrigan in character. Visible pulsation of the peripheral vessels was noted. Capillary pulsation was observed in the nail bed. The blood pressure in both arms was the same, 120 mm. Hg systolic and 10 mm. Hg diastolic.

The heart was greatly enlarged, the left border being 12 cm. from the midsternal line in the sixth left intercostal space. The supracardiac dullness measured 7 cm. A pronounced superficial systolic thrill was felt over the precordium, maximal in the third and fourth interspaces adjacent to the left border of the sternum. On auscultation over the aortic area a short systolic murmur was heard, followed by a long, loud blowing, diastolic murmur which was transmitted downward along the left border of the sternum toward the apex of the heart. Maximal, in the fourth left intercostal space there was heard an intense, superficial, rasping systolic murmur, which was transmitted well over the entire precordium. At this same area a diastolic murmur was heard. However, it was thought to have been generated at the aortic area. No edema was present.

A daily elevation of temperature occurred, usually reaching 100° F. The leukocyte count was 14,200, with 74 per cent polymorphonuclear forms. The blood culture was negative. A teleroentgenogram revealed the transverse inside diameter of the chest 28 cm., transverse diameter of heart at apex 17 cm. and aortic arch 7 cm. Fluoroscopic study of the heart and great vessels was not done. The electrocardiogram showed a moderate degree of right axis deviation and a sinus tachycardia. The Wassermann reaction on the blood was 4+.

**Course in Hospital.** In spite of rest in bed, digitalization and the other usual therapeutic measures, there was a progressive increase in the degree of cardiac failure. Edema of the lower extremities appeared along with an accumulation of fluid in the abdominal cavity and the right chest. Death due to cardiac failure occurred 15 days after admission.

The clinical diagnosis was congenital heart disease, with interventricular septal defect, syphilitic aortitis with extensive destruction of the aortic valves and possibly a subacute bacterial endocarditis.

**Necropsy.** The heart was about twice the normal size and showed rather marked dilatation of all chambers. The wall of the left ventricle was 1.5 cm. in thickness. The ascending portion and the arch of the aorta was the seat of a diffuse saccular dilatation which measured 10 cm. in its greatest diameter. The innominate and left common carotid arteries arose from the dome of the sac. A large mixed thrombus nearly entirely filled the sac.

Behind the right posterior cusp of the aortic valve the sinus of Valsalva was pouched out to form a small aneurysmal sac which extended down just posterior to the orifice of the pulmonary artery. The bottom of this sac opened into the cavity of the right ventricle through an aperture 1 cm. in diameter, which passed through the lower part of the posterior leaflet of the pulmonary valve. This leaflet was fairly adherent to the wall of the pulmonary artery at its base. The edges of the aperture were rounded and smooth, and it appeared to have been present for some time. There were no clots in this aneurysmal sac, which made it evident that blood passed freely from the aorta into the right ventricle during life. The aortic ring showed considerable dilatation. The aortic valves showed some thickening and rolling of the free edges. In the intima of the ascending portion of the aorta were found multiple linear and stellate scars. (See illustration.)



View from right ventricle, showing the conus arteriosus and the pulmonary valves. The perforation is seen in the lower portion of the posterior valve. (See arrow.)

The anatomic diagnoses were hypertrophy and dilatation of the heart, syphilitic aortitis and aortic valvulitis, aneurysm of the ascending portion and the arch of the aorta, aneurysm of the right posterior sinus of Valsalva with rupture into the right ventricle.

*Comment.* Aside from the chest pain, which was thought to be a result of the syphilitic aortitis, there was nothing in the history or physical examination to suggest the presence of an aneurysm. It was not visualized on the flat Roentgen ray plate because of the

fact that it extended in an anteroposterior direction. Fluoroscopy, had it been done, would have undoubtedly made the diagnosis because of the obliteration of the posterior mediastinal space.

**Discussion.** Rupture of a congenital aneurysm of one of the sinuses of Valsalva, usually the right, into the right ventricle has been reported several times. Abbott<sup>2</sup> reported a case and collected 7 others from the literature. An additional case, not included in Abbott's review of the literature, is reported by Gage.<sup>3</sup> The majority of these cases were associated with defects in the interventricular septum. Rupture of an acquired aneurysm into the right ventricle, however, is a much rarer condition, only 2 cases being found in the literature after a rather careful search.

Laycock,<sup>4</sup> in 1860, reported a case occurring in a man, aged 56 years, whose symptoms had been present for 4 months. There was marked cardiac enlargement, a visible aneurysm in the neck and a distinct thrill over the precordium which was associated with a loud, rasping, double murmur heard loudest over the aortic area. Death was due to progressive cardiac failure. At necropsy the entire aorta was found to be the seat of extensive disease, which, apparently from the description, was syphilitic in nature. A large fusiform aneurysm of the ascending aorta was present, from which a smaller sac had budded off and ruptured into the conus arteriosus of the right ventricle.

The other case was reported by Lichtenburg,<sup>5</sup> in 1865. It occurred in a young man, aged 29 years, who had been in apparent good health. The outstanding symptom was severe palpitation. A thrill over the lower region of the heart was present, and "each sound was replaced by a strong bruit." Death occurred 14 days after the onset of symptoms from heart failure. Postmortem examination revealed a "rounded aperture the size of a goose quill behind the posterior semilunar valve which opened into a sac the size of a filbert." The aneurysmal sac bulged into the right auriculoventricular opening and at one point had ruptured. From the description of the aortic valves and also the liver, syphilis seemed a likely etiologic factor.

The physical signs resulting from this abnormal communication between the two circulations are essentially the same as those described by Scott<sup>6</sup> where the aneurysm had ruptured into the pulmonary artery. An intense, superficial thrill was present in all cases. In the 2 previously reported cases the resulting murmur was continuous in character. In the case reported here the character of the murmur was somewhat obscured by the associated aortic insufficiency. The sudden establishment of the arterial venous shunt results in such marked disturbance of cardiac function that congestive heart failure appears rapidly and is the cause of an early fatal termination. In all cases syphilis was the etiologic factor in the production of the aneurysm.



**Summary.** A case of acquired aneurysm of the ascending aorta with rupture into the conus arteriosus of the right ventricle is reported. The resulting physical signs simulate very closely those of congenital heart disease. The 2 previously reported cases are briefly reviewed.

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### A CASE OF CONGENITAL STENOSIS OF THE PULMONARY VALVE, WITH LATE ONSET OF CYANOSIS: DEATH FROM CARCINOMA OF THE PANCREAS.\*

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OUR knowledge of the classification and physiology of the congenital cardiac anomalies has advanced remarkably during recent years, thanks to the excellent work of Abbott, Lundsgaard and others. One group of congenital cardiac cases which is of particular interest is that in which the cyanosis first makes its appearance some years after birth. We wish to report such a case that presents other points of unusual interest, among them being the fact that the cyanosis was not due to oxygen unsaturation of the arterial blood, and was limited to certain areas, thus giving the patient a striking and bizarre appearance.

\* Read before the Section on General Medicine, College of Physicians, May 26, 1930.

**Case Report.** The patient was born in Scotland of healthy ancestry and was not a "blue baby." There was nothing in his early life to indicate that he was abnormal. He was unusually athletic and a devotee of "soccer" and cross-country running. He saw 4 years of active service during the World War, and was known in his company as an excellent boxer, sometimes competing two or three times on the same night. Both during and after the war he underwent several thorough examinations, but was never led to believe that there was anything abnormal about his heart or his color. He came to America, in 1924, worked as a truck driver and was required daily to lift numerous heavy milk cans onto his truck. Dr. Robert L. Gray informs us that he examined the patient for insurance in 1925 and in 1928, and that on neither occasion did he note anything abnormal about the patient's heart or his color.

The patient stated that for 2 months prior to coming under our observation he had noticed swelling of the ankles at night and that he had more recently suffered from dyspnea. He was seen during 2 dyspneic attacks by Dr. Gray, who noted the usual signs of acute cardiac decompensation, together with a remarkable blue color of the skin. The patient was thereupon advised to enter the Episcopal Hospital, where he was first seen by us, in April, 1929. The blue color had first been noticed 2 years before, following an ocean bath at Atlantic City. At this time it wore off promptly, but returned whenever he was chilled or when walking against the wind, and in recent months it was noted continuously, though in varying degrees. He had never had sore throats, rheumatic fever nor chorea. He was not subject to colds during the winter and had never before had a serious illness. He was very temperate in his habits, using no tobacco and little alcohol. Because of his cyanosis, he was closely questioned regarding exposure to drugs, but we were unable to elicit a history of contact with or ingestion of any toxic chemicals or drugs.

Examination revealed a very well-developed and well-nourished young man, aged 32 years, lying quietly in bed without dyspnea, but with a remarkable bluish-purple tinge of the skin. The color was deepest in the face, where it was a splotchy purple, especially at the tip of the nose, the cheeks and the lobes of the ears. Looking more closely, it might be seen that this color was mainly or entirely due to the presence of engorged, deeply purple superficial bloodvessels, many of which were visible to the naked eye as loops or dots lying just beneath the surface of the skin. Microscopic examination of the finger by the Lombard method showed capillaries which were more numerous and more tortuous than one usually finds in normal subjects, some capillaries having as many as four loops visible. Portions of the trunk and extremities also presented a purplish appearance, but not to such a degree as the face. On stroking the skin, the finger left a blanched trail for a few seconds, this quickly gave way to a bluish discoloration, and this, in turn, was followed by a brick red color with blanched margins, the latter phenomenon lasting about 5 minutes. There was absence of cyanosis of the lips and finger-nail beds. The mucous membranes of the mouth were somewhat injected but not cyanotic, and the tonsils were small. The cardiac measurements as shown by a teleroentgenogram (Fig. 1) were: M. L., 10 cm.; M. R., 4 cm.; length, 16.3 cm.; arch of aorta, 5.5 cm.

Dr. Bromer, in commenting upon the appearance of the Roentgen ray, reported: "The 6-foot film shows slight increase in the width of the left ventricle shadow, also in the right auricle shadow. The appearance is more characteristic of mitral regurgitation than of pulmonary stenosis. There is no marked cardiac dilatation or hypertrophy present." Over the entire precordium there was a very harsh systolic murmur which was best heard at the third interspace to the left of the sternum, and was transmitted into the left axilla and to the left scapular angle. There was little or no

transmission to the vessels of the neck. No thrill was noted by us either while the patient was at rest or during exercise, but Dr. James Kay on one examination noted the presence of a systolic thrill near the apex after exercise. The pulse and respiratory rates respectively with the patient at rest were 88 and 18. After exercise his pulse rose to 112, the respirations to 22, but within 2 minutes his pulse fell to 88 and respirations to 20. The arterial blood pressure was 102 systolic and 68 diastolic. The venous pressure was not measured but no venous pulsation was present, and the veins of the hand were seen to collapse when the hand was raised to the level of the chin. The tourniquet test of capillary resistance (Rumple-Leede's phenomenon) was negative. The spleen was not palpable, the liver was felt about 3 cm. below the costal margin and was hard. The lungs were normal. Although the toes were a little clubbed, the fingers showed no clubbing. There was some edema of the ankles. The eyegrounds were reported by Dr. Fewell as normal in appearance. Blood counts were as follows:

Date, 1929.	R. B. C., millions.	W. B. C., thousands.	Polymorphonuclear neutrophils, per cent.	Hemoglobin per cent, (Dare).
April 26 . . .	4.5	6.4	73	70
May 10 . . .	5.0	11.5	68	85
May 13 . . .	5.0	11.0	71	80
Oct. 30 . . .	4.6	9.9	73	98

The urine was negative except for a faint trace of albumin. The Wassermann reaction of the blood was negative. The blood urea nitrogen was 33 mg. per cent, the plasma CO<sub>2</sub> was 40 and the fasting blood sugar 0.05 per cent. A glucose tolerance test showed some disturbance in the glycolytic function for 2 hours after the ingestion of the glucose solution, the blood sugar was 0.26 per cent and there was 1.1 per cent of sugar in the urine. The electrocardiogram showed right ventricular preponderance but was otherwise normal. (Fig. 3.) The vital capacity of the lungs was 3900 cc. (5 per cent below the expectation for one of his age, height and weight). The response of the skin of the forearm to needle pricks through solutions of adrenalin and also histamin was normal.

Thinking that perhaps a communication might exist between the right and left cardiac chambers, which, under conditions of increased pulmonary pressure, would allow the entrance of venous blood into the arterial circulation, a test was devised which it was thought would artificially increase the pressure within the right cardiac chambers. The patient was instructed to inhale, and while attempting forced exhalation through a mouthpiece ending in a mercury manometer, the skin of the body was scrutinized for any evidence of increase in the cyanosis. Several prolonged efforts at exhalation, registering pressures of 20 to 50 mm. of mercury, failed to produce any noticeable deepening of cyanosis, and it was concluded that this was evidence against the presence of a communication between the right and left cardiac chambers of sufficient size to be of physiologic importance.

*Course.* On rest and digitalis therapy the edema of his ankles disappeared and about 1 month after admission he asked for his discharge. Two days before leaving the hospital, however, he developed diarrhea.

Late in the summer we both had the opportunity of seeing him at his home, and learned that the diarrhea had never ceased, there being eight to ten watery bowel movements a day, though he never passed any blood. He had lost a great deal of weight, was quite weak and had curious seizures of shortness of breath, choking cough and at times irrational periods in which he went over some of the events of his life in the army, frequently giving military commands to imaginary forces. These cerebral

attacks at times lasted all night, leaving him rational in the morning, without any memory of their occurrence. The liver had become more enlarged, its edge being at the level of the umbilicus; it presented a smooth surface under the palpating hand. The skin of the legs was tense and shiny. Some weeks later he developed weakness of the left leg, with exaggeration of the patellar reflexes and bilateral ankle clonus and Babinski reflexes. Three days before death he was readmitted to the hospital, aphasic, a little agitated, in a semidelirious state. Dr. George Wilson made the following note on November 1, 1929: "Bilaterally increased reflexes; Babinski, ankle and patellar clonus. Myoclonic twitchings of both hands and the right side of the face suggestive of cortical irritation. He attempts to obey simple commands but is speechless. The neck is stiff. The presence of bilateral signs with muscular twitchings, the predominance of motor weakness in the lower extremities and the cerebral disturbances point to a thrombosis of the longitudinal sinus."

The patient died on November 3, 1929, and an autopsy was performed on the same day by Dr. John Klopp.

*Autopsy.* Only the significant findings will be reported. On opening the chest the right side of the heart seemed dilated. The organ weighed 205 gm. and measured 13 by 9 by 4 cm. The epicardium was pale and glistening. There was a slight excess of subepicardial fat. The right ventricle measured 6.5 by 9 cm. and the left 4 by 9 cm. The sizes of the various orifices were as follows: Mitral, 8.5 cm.; tricuspid, 9 cm.; aortic, 6.4 cm.; pulmonary, 3.5 cm. The endocardium presented a normal appearance and no evidence of valvulitis was present. No interventricular septal defect was found. A probe could be passed through the foramen ovale, but the latter was guarded on both sides by large folds making it, in the opinion of those who saw it, anatomically patent but functionally closed,\* so that in the opinion of the pathologist there was no functional communication during life between the auricles. The wall of the left ventricle was 1.4 cm. thick and that of the right 0.6 cm. Both auricular walls measured 14 mm. The heart muscle was dark red, and histologically showed hypertrophy and edema. There were a few yellow plaques in the aorta. The pathologic diagnosis was congenital pulmonary stenosis; hypertrophy and dilatation of the heart.

The pancreas measured 12 by 4 by 3 cm., was of a yellowish color, firm consistency and contained several nodules in its head which macroscopically suggested neoplasm and microscopically proved to be adenocarcinoma.

The liver weighed 2200 gm. The surface was smooth and the edge sharp. It was studded throughout with yellow umbilicated circumscribed lesions of metastatic adenocarcinoma. The lymph nodes about the cystic duct showed carcinomatous infiltration but had not obstructed the flow of bile from the gall bladder. There was a mass of retroperitoneal lymph nodes infiltrated with carcinoma. Evidences of metastasis within the lungs were carefully sought for, but not found.

The brain failed to show any lesion except axonal chromatolysis and ischemic cell disease. The longitudinal sinus was not thrombosed.

The *histologic* examination of the specimen of the skin showed some thinning of the superficial layers and an increase in the amount of loose fibrous tissue present. There was an increase in the number of bloodvessels, the walls of the latter being greatly thickened. (Fig. 2.)

**Discussion.** In spite of the late onset of cardiac symptoms, it is hard to conceive that the pulmonary stenosis could have been other

\* A slitlike opening in the fossa ovalis has been found to be present in somewhat over 30 per cent of adult hearts. (Piersol.)

than a congenital anomaly. No pathologic evidence of an inflammatory process either recent or remote was found, nor did the history point toward rheumatic fever or any illness which might lead to a valvular lesion. While other writers have reported cases of congenital pulmonary stenosis which lived longer or developed cyanosis later in life than our patient, we know of no instance where the victim of this cardiac anomaly showed special athletic prowess; on the contrary, most cases have been found to adopt a sedentary mode of life. Death from carcinoma is also an unusual finding, the commonest causes of death in congenital pulmonary stenosis being pulmonary tuberculosis and bacterial endocarditis.

The cyanosis in this case differed in appearance and distribution from that caused by cardiac decompensation. It was not due to oxygen unsaturation of the arterial blood, for, as has been said, the finger-nail beds and lips were not cyanotic; furthermore, Dr. Leon Collins found that in a sample of blood from the radial artery the oxygen saturation was normal (oxygen content, 17.6 volumes per cent; oxygen capacity, 18.6 volumes per cent; the oxygen saturation, therefore, 94.6 per cent).

In contradistinction to that ordinarily seen in cardiac decompensation, the cyanosis in our case was limited to certain localities of the skin. Local cyanosis is seen normally as a result of exposure to cold, and pathologically in a number of conditions, including erythromelalgia and Raynaud's disease. It is due to increased oxygen consumption in the capillary bed due to venous stasis (Lundsgaard's D factor), thus rendering the blood within the capillaries similar to venous blood as regards color and oxygen content. The cause of the venous stasis in Raynaud's disease, according to Lewis, who has recently made an exhaustive study of the subject, is arterial spasm. Where the fingers are involved by cyanosis in their entire length, he asserts that the vessels implicated are the digital arteries in their entire length. In our case the stasis was caused, or at least accompanied by a dilatation of the superficial vessels of certain areas of the skin, notably the nose, cheeks and portions of the anterior aspect of the trunk, and to a lesser extent the upper extremities.

Morgagni was the first to recognize the fact that certain cases of congenital heart disease owed their color to dilatation of the skin vessels, and cases of congenital heart disease have been reported by Carpenter and others, where not only the skin but also the internal viscera partook of such vascular dilatation. Vascular dilatation was carefully sought for in sections of the visceral organs removed at autopsy, but was not found in our case. Just what the relationship of dilated bloodvessels and congenital heart disease may be is a matter for speculation. We feel, however, that the fact that this combination has been described previously renders it unlikely that it is merely coincidence either in our own case or in the others reported in the literature.



FIG. 1.—Teleroentgenogram of a case of congenital stenosis of the pulmonary valve, showing slight increase in the width of the right auricular and left ventricular shadows. Prominence of the pulmonary arc, usually found in cases of congenital pulmonary stenosis, is absent in this case.

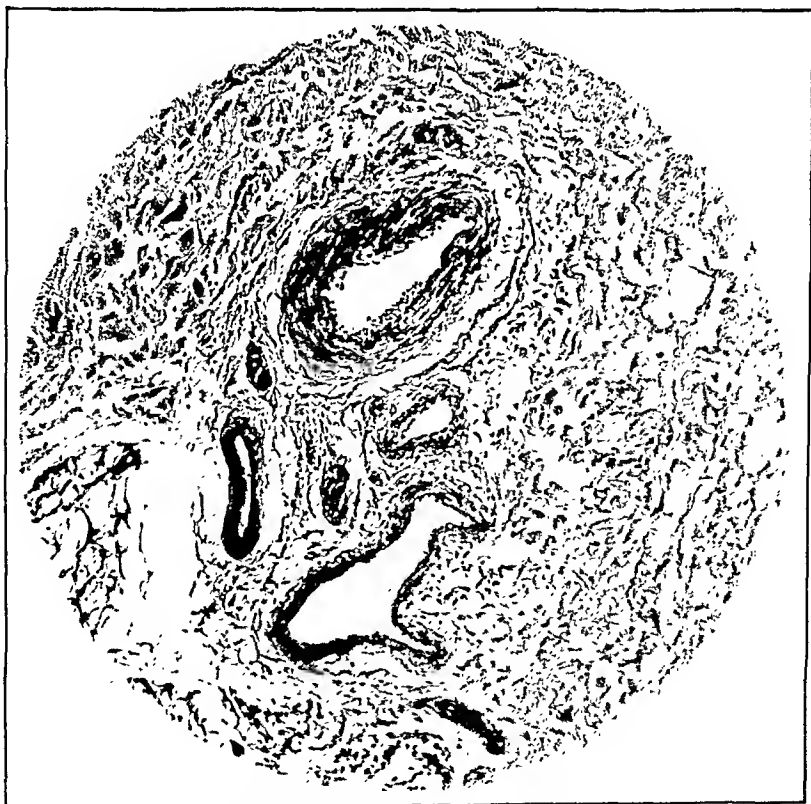


FIG. 2.—Section of skin (magnified  $\times 80$ ), showing numerous bloodvessels with thickened walls. The localized cyanosis in this case was presumably due to the presence of numerous dilated superficial bloodvessels in certain localities.

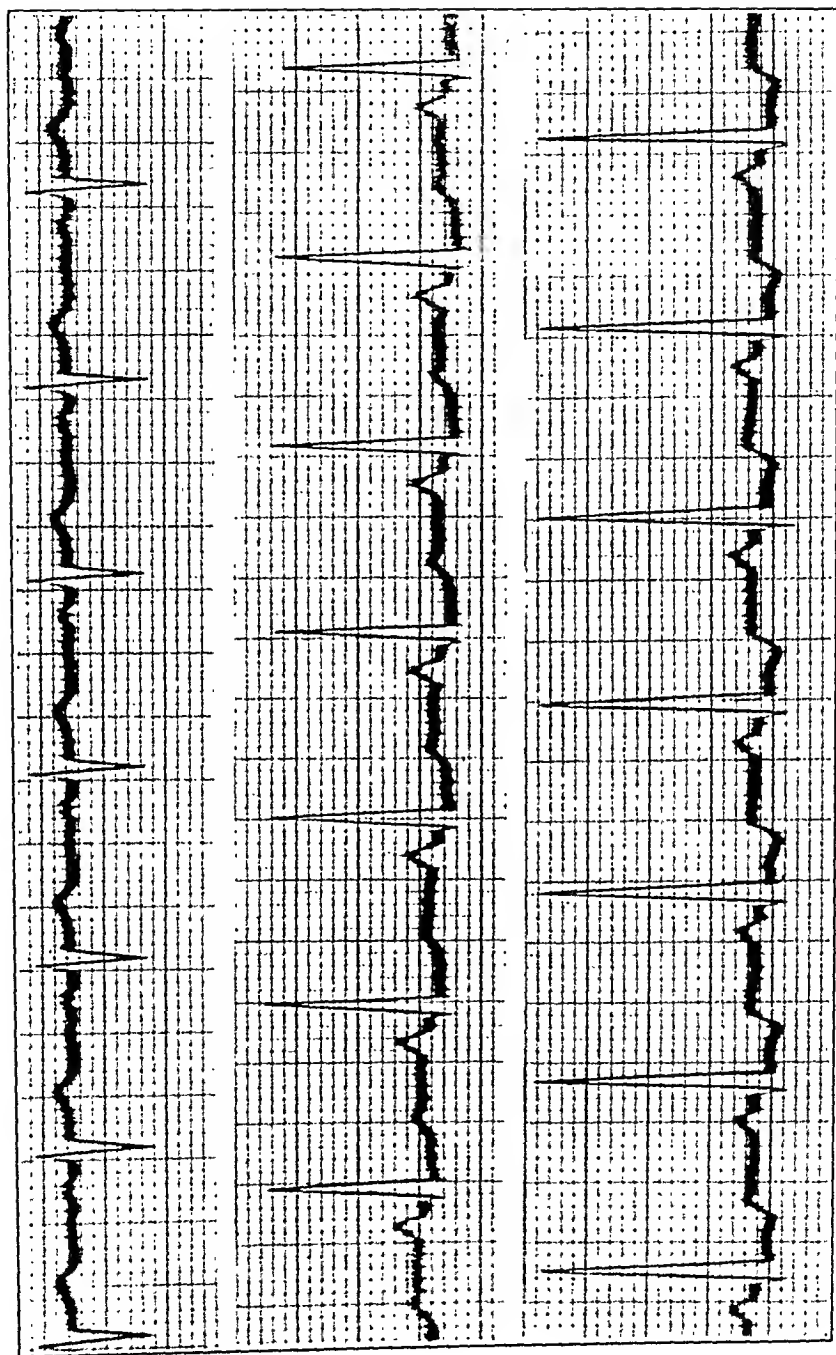


FIG. 3.—Electrocardiogram, showing the right axis deviation usually present in congenital pulmonary stenosis. (Chief ventricular deflections intensified with India ink for clearer reproduction.)

**Summary.** The case of a patient with simple congenital pulmonary stenosis is presented, who after an exceptionally athletic career gradually developed localized areas of cyanosis believed to be due to the stasis of blood within dilated minute bloodvessels of the skin. Attention is called to the fact that cyanosis due to vascular stasis is not uncommon in congenital cardiac disease, and occurs in other conditions as well. Death in this case came at age 33 as a result of carcinoma of the pancreas, an unusual complication of congenital pulmonary stenosis.

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### POSTURAL HYPOTENSION: A CASE REPORT.\*

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WITH the recent case of Riecker and Upjohn,<sup>1</sup> 8 cases of marked postural hypotension have been reported: 3 by Bradbury and Eggleston,<sup>2</sup> in 1925, 2 by Ghrist and Brown,<sup>3</sup> in 1928, and 2 by Vaughan<sup>4</sup>, in 1928. Another case of marked postural hypotension with the characteristic syndrome is here presented.

In this case, as in the previous cases, the symptoms of anemia of the brain came regularly with the upright position and promptly disappeared with the lowering of the head to the body level, these phenomena recurring quite constantly over a period of years.

**Case Report.** The patient, a successful attorney, aged 34 years, came under observation in September, 1930, complaining of dizziness, faintness and mental haziness, that came on when he continued in an upright position for any extended period, of chronic edema of the feet and legs below the knees and of chronic diarrhea, with two or three watery stools a day.

The observation period ended on October 11. The following notes are from the case records: He states that he was very active and enjoyed good health in childhood and in youth until he was 21 years of age. During the fall and winter of 1917-1918 he was exposed to cold and hardships. He developed a severe cough and became generally run down, though he continued at rather exacting and exhausting duties. In April, 1918, while already in a weakened and much fatigued condition, he attempted to tramp some 9 miles, carrying a heavy load on his back. Near the end of this

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journey it became necessary for him to run for some distance up a small hill. As he ran he suddenly had the sensation as if something had broken loose low down in his abdomen. He fell to the ground, but did not become entirely unconscious. After about 10 days' rest he felt much better and resumed his duties. However, to the patient's own mind, all his later physical troubles had their beginning when he felt that "something" break loose in his abdomen. Always after that he had a constant dragging sensation in the lower abdomen, and he never again regained his normal strength. During the following August he developed a severe diarrhea with abdominal cramps and frequent watery stools, but he still continued at his duties. One day, about this time, as he jumped from a truck to the ground he had a sudden feeling of extreme faintness and as if his abdominal organs were sinking down. At the same time he had pain and a queer feeling in the sacroiliac region and in the hips and legs. Though he was faint at this time, he did not lose consciousness. He had another and similar attack during October, 1918. In this attack, which also occurred as he jumped from a truck to the ground, he thinks that he actually lost consciousness for a few minutes. After that he had frequent periods of great faintness and dizziness whenever he continued for a long time in an upright position.

The diarrhea with watery stools continued from the summer of 1918 until 1922. Then, for 5 years, from 1922, to 1927, he was fairly free from the diarrhea; but in 1927 it returned, and most of the time since then he has had two to five watery stools each day. He has had no periods of constipation. He has not been subject to abdominal cramps in recent years, but he often has a "sinking sensation" in the abdomen. Associated with the evacuations of the watery stools, he frequently has a distress which he describes as deep in the abdomen, "in the sacroiliac region." He has never lived in the tropics, and he has never been told that any pathogenic intestinal parasites have been found in his feces, though his feces have often been examined for parasites.

His faintness and dizziness have been an increasing handicap during the years since 1918. However, he fitted himself for the profession of law, and for the past 5 years he has been quite successful in the practice of that profession, in spite of his handicap. For some years he has spent the greater part of his waking hours lying on a couch, in the prone position, with two or three cushions under his abdomen. In this position he carries on most of his professional work. He states that, with his body in this position, he can continue very exacting mental work for hours without fatigue. But his mind becomes fogged, his sight becomes blurred and his speech is stumbling after a period, maybe of only a few minutes, in a sitting or standing position. Walking or riding is even worse. However, immediately he lies down his thought, sight and speech becomes normal. In the courtroom he has found that he is at his best in very short cases or in cases where frequent recesses are granted, and that he is at a great disadvantage when he is forced to continue on his feet or in a chair. At such times, when he feels his mental faculties failing, he is apt to lose his self-control and, in attempt at self defense, is apt to resort to bitter and stinging words. He has often made further trouble for himself in this way. He has many times fallen in a semiconscious condition when he has forced himself to continue upright. On one occasion, in 1923, while working in his garden, he became faint and stumbled and seriously sprained or fractured his left foot. One evening, about 2 years ago, while walking the short distance from his office to his home, he became very tired and faint and fell, fracturing his right femur. However, it appears that at no time have these attacks been of a nature to raise the question of epilepsy.

Throughout these years the patient has noted that his pulse has been

slow, this more especially when he has been tired. He has also observed that with exertion or excitement his pulse has become slower rather than faster. He has noted, too, that his pulse has often been irregular and that this irregularity has been particularly apt to occur when he has been resting. A few years ago a physician gave him atropin medication for a short time. He felt rather better while on this treatment, but he states that he discontinued the atropin for the reason that he found his judgment was faulty while he was under its influence.

He gives no report of having had any definitely localized precordial distress, though for years he has been troubled with various chest pains, presumably of the nature of pleurisy. When very tired he has occasionally been troubled with a severe pain in the left forearm, wrist and palm. This pain has come "with startling suddenness and severity" and has, at time continued for as long as a half hour. At no time has this pain been associated with any chest pain. He has had no such pain in the right arm, wrist or hand.

For many years it has been the common observation of his family and his friends that he becomes very pale soon after he sits up or stands up and that his color becomes normal almost immediately with his lying down. He has observed for the past 8 or 10 years that his feet and legs have ordinarily been somewhat edematous and that they have become heavy and numb after walking a few blocks. He has not observed his hands or feet to be cyanotic or excessively damp or cold. He sleeps habitually with his face downward. He uses no pillow under his head, but he regularly sleeps with two or three pillows under his abdomen. He is not subject to night dyspnea, and ordinarily he has no nocturia.

The patient gives no report of having had rheumatic fever, chorea, scarlet fever or diphtheria and he emphatically denies all venereal infections. He gives no definite history of any serious respiratory disease during recent years. He was subject to occasional attacks of tonsillitis prior to tonsillectomy in 1921. He has used liquor very moderately and he smokes but two or three cigars a day. He denies ever having used drugs, and there is nothing in his records or in his personal appearance that is suggestive of drug addiction.

*Family History.* The patient's father and mother are both living and in fairly good health. He has 3 brothers and four sisters living and well. Two sisters died in childhood and 1 sister died in adult life, of cancer. The patient has been married since 1921. The wife is well. By this marriage she has had 2 early miscarriages and 4 children at term. The children are all normal and well.

*Physical Examination.* The patient is a slender, poorly developed and poorly nourished white man, 72½ inches tall and weighing 150 pounds, who had the appearance of his stated age of 34 years. His gait and movements are fairly active. He is evidently of an intellectual type and he seems to be mentally alert, but he has a melancholy expression of countenance. He sways notably when standing with eyes closed. He has a rounded upper dorsal stoop and slight lumbar lordosis; he seems to be unable to stand perfectly erect. The chest is of long type and is poorly developed, but symmetrical. The scapulae are somewhat winged. The abdomen is long, flat and sagging. He has very slight tremors of the extended fingers. The fingers are not clubbed. The finger nails are quite normal. Flexion of the right hip is markedly limited. (History of fracture of neck of femur 2 years ago.) The patellar reflexes are active. The left foot is somewhat misshapen. (History of injury in 1923.)

When the patient is in the upright position his face, ears, neck and upper chest are ghastly pale and he has the appearance of one who is very ill or about to faint. However, when he lies down he immediately has a

perfectly healthy color. His skin is smooth, soft, normally moist and free from lesions. No gross scars of operations or injuries are noted. There is no cyanosis of the dependent hands or feet. The hands become quite white when they are elevated for a few moments. No varicosities are observed. Both legs below the knees are distinctly edematous and pit markedly with pressure.

His hair is thick, dark and glossy. His face is symmetrical. He wears glasses. He has no exophthalmos. His pupils are equal and regular and react to light, accommodation and convergence. The teeth and gums are well kept. The tongue appears normal. The breath has an extremely fetid odor. The thyroid appears normal and the superficial lymph nodes appear normal.

*Summary of Further Observations.* No definite evidences of disease were found in the upper respiratory tract. The physical and Roentgen ray findings of the lungs were essentially negative. The heart was found to be rather small and centrally placed. No precordial thrills were palpated. The cardiac sounds were somewhat muffled. No cardiac murmurs were heard. The rhythm varied with repeated examinations. At times the rhythm was perfectly regular; at other times marked sinus arrhythmia was observed; occasionally extrasystoles were noted. Repeated electrocardiograms gave no additional evidence except to show that the extrasystoles were ventricular in origin. The pulse rate was found as low as 40, though usually the range was 50 to 60 when the patient was lying down and 60 to 70 when he was sitting or standing. With the exercise of 100 hops the pulse rate of 48 (recumbent) was reduced to 45 (recumbent), and 2 minutes later the rate continued at 45. Firm pressure on the eyeballs caused no definite change in the pulse rate. Firm digital pressures, alternating on the right vagus and on the left vagus nerve in the neck, caused absolutely no change in the pulse rate. Later, the patient was given full doses of tincture of belladonna for a period of days. During this period the pulse tended to remain at the lowest rate rather than to increase.

The blood-pressure reading was 130 systolic and 74 diastolic with the patient in the sitting position and the arm hanging by his side. The arm was raised so that the elbow was at the level of the upper thorax and the blood-pressure reading was 110 systolic and 68 diastolic. The arm was then elevated so that the sphygmomanometer cuff was at the level of the head and the reading was 84 systolic and 60 diastolic.

With the patient standing, the abdomen was notably sagging in appearance. No abdominal masses were palpable and no abnormal tenderness was elicited by deep palpation. Firm pressure on the abdomen or a tight abdominal belt caused a lessening of the patient's dizziness.

*Laboratory Data.* Blood: Hemoglobin, 100 per cent; total red blood cells, 4,800,000 per c.mm.; total white cells, 8200; polymorphonuclears, 65; small mononuclears, 27; large mononuclears, 3; transitionals, 2; eosinophils, 2; basophils, 1. Blood sugar, 95 mg. Blood Wassermann reaction negative. Icterus index, 4. Van den Bergh test: Direct, negative; indirect, normal. Three basal metabolic estimates averaged -17, but the readings were not considered entirely satisfactory.

Gastric analysis was omitted because of the difficulty the patient experienced in attempting to take the tube. Ten sputum reports were negative. Urinalysis reports were normal. The feces were of liquid consistency. Traces of occult blood were reported. Endolimax nana and blastocystis hominis were found.

The Roentgen ray report of a gastrointestinal series, including barium enema, reads in part: "Haustra are poor in the transverse colon and practically absent in the descending colon and sigmoid. This is presumptive evidence of ulcerative colitis."

**Comment.** It is of special interest in the case of this young man with the characteristic syndrome of marked postural hypotension that his symptoms began on a definite date with a definite experience. It seems reasonable to assume that a lesion of the autonomic system was incurred at that particular time.

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## THE LEUKOCYTIC REACTION IN TUBERCULOSIS OF INFANCY AND CHILDHOOD.\*

### BLOOD STUDIES WITH THE SUPRAVITAL TECHNIQUE.

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THE introduction of the cutaneous tuberculin test by Pirquet, in 1907, revealed the frequency of tuberculous infection in infancy and in childhood. A positive reaction, while more significant than in the adult, is not so readily appraised when considered in terms of the activity of the existing lesion. Of the laboratory aids available for evaluating more precisely the activity of tuberculous infection, the white blood count has of late been restored to a position of importance. It is the purpose of this paper to present a preliminary report, based on studies of the peripheral blood carried on during the past two years, in which the newer technique has been employed.

Although the white blood count has been related in the past with stages of resistance and activity in tuberculosis, it is only recently that it has been interpreted as reflecting the pathological state of the tuberculous lesion. This largely resulted from the added information acquired concerning the principal cell types involved in the tissues and organs in this disease. In 1925 Sabin and her

\* Read before the Combined Meeting of the Philadelphia and New England Pediatric Societies and the Pediatric Section of the New York Academy of Medicine, New York City, October 11, 1930.

coworkers,<sup>1</sup> on the basis of observations in experimental tuberculosis in rabbits, in which the supravital technique was used, concluded that the major effect of the tubercle bacillus was on the monocyte of the connective tissues and blood. Within the monocyte the tubercle bacillus may grow and multiply, while the lymphocyte they found to be intimately connected with limiting the spread of the infected monocytes in the tissues. The predominating reaction within the tissues could be measured in the peripheral blood by the numerical preponderance of either type of cell and might be expressed by the ratio of monocytes to lymphocytes as obtained from a differential smear and total white count.

These observations were soon thereafter confirmed in studies of tuberculous children<sup>2,3</sup> and adults.<sup>4,5,6,7</sup> The results based on supravital and fixed smear determinations demonstrated that in clinical tuberculosis activity was indicated in the peripheral blood by an elevation of the monocyte count. A reversal of the normal ratio of monocytes to lymphocytes indicated extension of the process. When arrest or healing takes place in the tissues the lymphocytes are found to be increased in the circulating blood, the monocytes decreased and a more normal ratio is reestablished. In the periodic determinations of the leukocytes Medlar<sup>8</sup> stresses the importance of including the polymorphonuclear neutrophil, which he regards as chiefly responsible for tuberculous abscess formation.

In the present study the general leukocytic reaction in various forms of tuberculosis of infancy and childhood was investigated. Attention was directed not alone to the monocyte count and monocyte to lymphocyte ratio, but to changes in the other cell types as well. The supravital technique of Sabin<sup>9</sup> was used throughout to enable examination of the cells in the living state instead of their altered forms after fixation. As shown in a previous study,<sup>10</sup> the percentage of polymorphonuclear neutrophils to lymphocytes is higher with this technique than in the fixed smear. With the supravital method also, cell differentiation is facilitated particularly as it applies to the monocyte and its derivatives, and to the eosinophilic leukocyte.

The monocyte represents the transitional cell of the Ehrlich classification, and includes the large mononuclear cell as well. It is now recognized as a cytologic strain distinct from the polymorphonuclear leukocytes and lymphocytes. In the living preparation after contact with the neutral red dye this cell is found to possess an eccentric nucleus. Near the indentation or "hof" of the nucleus are observed fine salmon-tinted bodies arranged usually in a characteristic rosette about an unstained area or centrosphere. Sabin<sup>9</sup> observed that following the ingestion of the tubercle bacillus by the rabbit the monocyte in the circulating blood loses its motility, the number of stainable vacuoles in the cytoplasm is increased and the cell is designated as stimulated or modified. The succeeding

steps in the pathologic transformation of the monocyte are the development of the epithelioid cell and later the Langhans giant cell. The stimulated monocyte and, less frequently, the epithelioid cell were observed in the supravital film in the active cases of this series. In the fixed smear these derivatives of the monocytes cannot be identified.

The present study includes a report of 291 supravital counts on 93 infants and children, 50 of whom served as a normal group. A summary of the results are here presented instead of the analysis of the complete data which will be the subject of a later communication. In general, these studies indicate that an increase in neutrophilic leukocytes and monocytes bears an important relationship to activity and extension of the tuberculous process and that the lymphocyte is associated with resistance.

**Normal Group.** In analyzing pathologic blood counts the high lymphocytic percentage of normal children must always be considered. Before an increased lymphocytic value in a tuberculous child can be regarded as evidence of healing or resistance, comparison must be made with the blood of a normal child of the same age. Except for the studies of Forkner<sup>11</sup> on newborn infants, the data available for older infants and children with the supravital method are limited. The peripheral blood of 50 normal infants and children was, therefore, examined in 88 determinations on one or more successive days and the average figures were recorded. Each child in this class was negative to 0.2 mg. of tuberculin, and in the group under one year this was carried to 2 mg.

It is observed that the average normal ratio of monocytes to lymphocytes (M/L) increases with age from 0.09 to 1 in infants under one year to 0.25 to 1 in children over the age of four years (Table I, last column). While the control series is small, the averages compare favorably with the estimated normal figures reported by Blackfan and Diamond<sup>3</sup> from fixed and supravital smears.

**Acute Tuberculosis.** A total of 17 cases comprises this group in all but 3 of which meningitis accompanied miliary tuberculosis. The children varied in age from five months to six years. In this type of tuberculosis the total white count is elevated, especially at the termination. The neutrophilic leukocytes and monocytes are increased while the lymphocytes are decreased. Stimulated monocytes were of frequent occurrence in the blood of the acute cases, but epithelioid cells were observed less often than in the animal experiments. The reason rests, doubtlessly, in the massive doses of organisms experimentally injected into the rabbit as compared with the smaller dosage in human cases. Diagnosis was at times possible from the increased monocytic percentage and the presence of stimulated forms in the peripheral blood previous to the report of other laboratory tests.

TABLE I.—NORMAL FIGURES.

	Age.	Total white count.	Neutrophilic leukocytes.		Eosinophilic leukocytes.		Basophilic leukocytes.		Lymphocytes.		Monocytes.		Monocyte to lymphocyte ratio (M/L).
			Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	
Extremes.	2 wks. to 11 mos.	10,175	37.9	3856	3.9	397	0.04	4	53.3	5423	0-10	0-976	0.02-0.24
Average.	1 to 2 yrs.	10,758	34.85	3749	4.63	499	0.17	18	51.12	5499	4.9	499	0.09
Extremes.	2 to 3 yrs.	9,211	45.8	4219	2.82	260	0	0	44.22	4073	6.5-12.0	754-1309	0.12-0.24
Average.	3 to 4 yrs.	9,065	51.17	4913	1.42	128	0	0	37.24	3374	9.23	993	0.18
Extremes.	4 to 11 yrs.	8,167	53.78	4392	5.04	412	0.07	6	32.87	2684	3.5-9.5	404-892	0.09-0.21
Average.	.....										7.16	659	0.16
											6.0-9.0	416-885	0.13-0.03
											7.17	650	0.19
											6.0-12.0	441-977	0.15-0.37
											8.24	673	0.25

TABLE II.—DIFFERENTIAL COUNTS IN CASE G. W., ACUTE MILIARY TUBERCULOSIS.

Date.	Remarks.*	Total white count.	Neutrophilic leukocytes.		Eosinophilic leukocytes.		Lymphocytes.		Monocytes.		M/L ratio.
			Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	Per cent.	Total.	
12/11	Temperature 101; feedings taken well; child alert	15,340	69.0	10,585	1.0	153	12.0	1841	18.0	2761 (includes 1534 S.M.; † 153 Ep. ‡)	1.5
12/13	Temperature 101.4; child still alert	15,200	76.0	11,552	0	0	12.0	1824	12.0	1824 (includes 456 S.M.; 304 Ep.)	1.0
12/15	Temperature 103.2; child drowsy and irrational	24,100	75.0	15,825	0	0	8.0	1688	17.0	3587 (includes 2532 S.M.; 211 Ep.)	2.12
12/16	Drowsy and irrational	22,500	78.0	17,550	0	0	8.0	1800	14.0	3150 (includes 1125 S.M.; 225 Ep.)	1.75

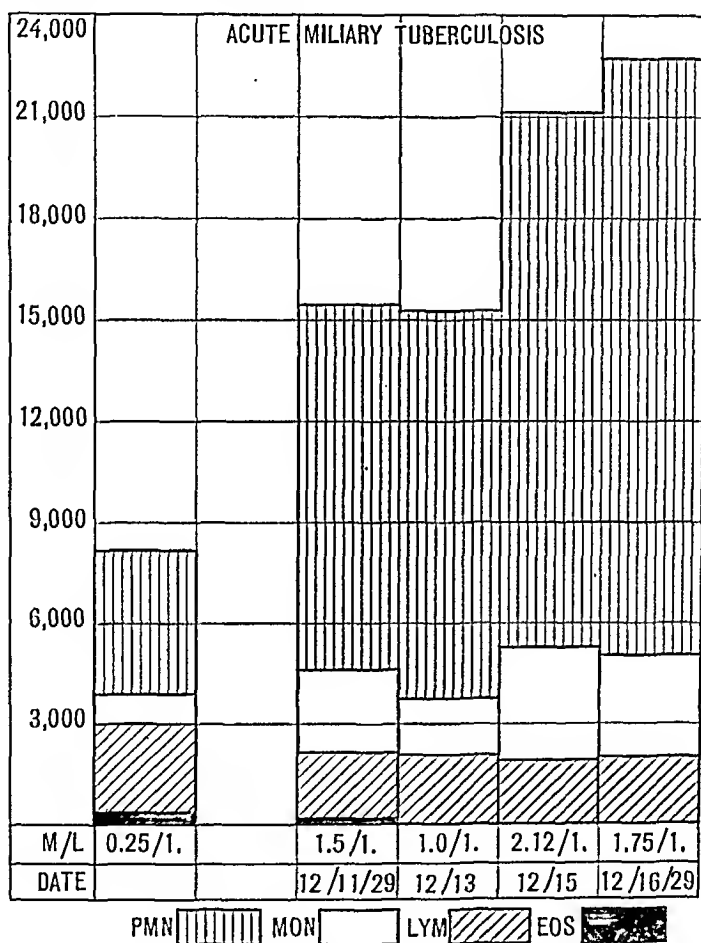
\* Died 12/20/29; tuberculin markedly positive 12/4. Roentgen-ray, 12/9, showed generalized milinary tuberculosis. Case uncomplicated by meningitis.

† S.M. = Stimulated monocytes.

‡ Ep. = Epithelioid cells.

The following case illustrates the chief features of this familiar form of tuberculous infection:

Case Report—G. W., a colored female child, aged four years, had been exposed to a tuberculous father. Two months before admission (December 5, 1929) she complained of acute abdominal pain. This symptom in less degree persisted throughout the illness. During this time an evening rise of temperature was noted accompanied by loss of weight, anorexia and loss of energy. In the hospital the child was alert and took her feedings well for the first ten days. Subsequently, she became drowsy, irritable, dyspneic and death occurred fifteen days following admission. Diagnosis: Miliary tuberculosis without meningitis.



Changes in peripheral blood of case G. W., aged four years (see Table II).  
The first column represents the average normal values for this age group.

*Comment.* This case portrays the characteristic blood picture of acute miliary tuberculosis. The total white blood count was elevated, the neutrophilic leukocytes and monocytes were increased in both percentages and absolute numbers, the lymphocytes were considerably decreased with a resulting high M/L ratio. Stimu-



lated monocytes and epithelioid cells probably active in tissue lesions were present in the circulating blood.

Translated into terms of individual cell function as it applies to tuberculosis, the leukocytosis and increase of polymorphonuclear neutrophils probably signify a spread of activity as well as a response to the liberation of toxic products, the monocytosis the formation of new tubercles and the fall in lymphocytes, the inability to restrain their multiplication. It is noteworthy that for a time the patient's clinical condition belied the severity of the infection as indicated by the blood smear. This observation is not uncommon, and emphasizes the fact that the blood picture reflects the activity of the tuberculous lesion and neither harmonizes with the clinical appearance of the patient nor with the roentgenographic evidence. It is believed by many observers that with certain restrictions, fluctuations in the blood picture of a tuberculous subject provide a more accurate index of what is taking place in the tissues than can be determined from physical or roentgenologic examinations. An isolated blood count, however, indicates the pathologic state only at the time when the specimen is secured and becomes increasingly valuable by comparison with differential counts taken at other periods.

In this group, the increase in polymorphonuclear neutrophils seemed to occur as a toxic manifestation of the disease. Medlar's view,<sup>8</sup> that this cell responds to abscess formation, may be tenable in the adult form of the disease. It does not apply, however, with equal force to tuberculosis of early life, since abscess formation is rarely present at this age period. The disappearance of the eosinophilic leukocyte occurred almost universally in the fatal cases of this series.

In the acute cases the supravital film frequently gave evidence of pronounced vacuolization and disintegration of the leukocytes with most marked injury to the granulocytes. After an initial phase of increased activity on the part of the polymorphonuclear neutrophil, loss of motility followed and then early disintegration of the cells. The monocytes and lymphocytes were less often affected, whereas the eosinophil shared the fate of the neutrophilic leukocyte. Strands of fibrin became visible and the field seemed to lose its transparency and to take on a ground-glass appearance. This phenomenon was not confined to cases with high fever, but was observed also in cases with a subacute or chronic course in which the temperature was slightly elevated. Vacuolization as well as clumping of the granules in the cytoplasm of the neutrophilic leukocytes have been observed in the fixed smear in infectious diseases and tuberculosis by Mayer.<sup>12</sup> These leukocytic changes may be associated with an immunologic response.<sup>13</sup> The increased fibrin deposit noted in the living preparation may be a counterpart of the increased sedimentation rate observed in tuberculosis<sup>14</sup> for which an increased fibrinogen content of the blood is held accountable.

**Subacute and Chronic Tuberculosis.** In this group are included 10 cases: 3 of pleurisy, 2 of epituberculous infiltration and 5 extrapulmonary forms, such as erythema nodosum, tuberculous dactylitis, tuberculosis of the spine and ischio-rectal abscess with fistula.

The extrapulmonary forms presented in general low or slightly elevated M/L ratios (usually three times as many lymphocytes as monocytes), as well as an absence of stimulated monocytes. In an infant, aged twenty-two months, with erythema nodosum the index was elevated during the period of the eruption and returned rapidly to normal when the skin lesions disappeared.

Tuberculous pleurisy need not necessarily be associated with striking blood changes. In 1 of the cases, however, the period of acute illness was accompanied by an increase of polymorphonuclear neutrophils, a slight decrease of eosinophils and an increased M/L ratio together with stimulated monocytes, constituting the cytologic evidences of activity. With the subsidence of the symptoms and disappearance of the signs, the blood assumed a more normal differential formula.

In 2 cases of epituberculous infiltration periodic blood examinations were often the sole index of changing activity. In 1, a child, aged twenty months, the Roentgen ray picture resembled in many respects that of miliary tuberculosis. The evidence obtained from the examination of the peripheral blood, however, indicated only moderate activity on admission, and the blood count became normal long before the roentgenogram began to clear. In the second case, that of a negro child, aged three years, the pulmonary condition followed closely the description of Eliasberg and Neuland.<sup>15</sup> Death from a probable tuberculoma of the brain ensued six months after the onset of the illness. In the interval the right lung was the seat of massive infiltration, and it was difficult from the Roentgen ray and physical examination to determine the progress of the disease. Blood examination from time to time showed significant deviations from the normal as represented by slight to moderate elevations in the M/L ratio and by an increase in the number of neutrophilic leukocytes. With the advent of the terminal cerebral complication, the monocytes became more numerous, stimulated forms made their appearance, the lymphocytes became fewer, the neutrophilic leukocytes were more prominent and the eosinophils disappeared, the typical picture of marked activity.

**Latent Tuberculosis.**—In this group have been placed 16 infants and children who reacted positively and usually to intense degree to low dilutions of tuberculin. Many of the children were admitted to the hospital for observation in order to determine the relation of known tuberculous infection to such symptoms as cough, undue fatigue, convulsions and gastrointestinal disorders. A small number were out-patient cases whose only abnormality was the positive tuberculin reaction.

In the ambulatory patient of this group information of practical value may be derived from blood examinations taken at regular intervals. Knowing what the count has been when the child was well, fluctuations in the different cell types during intercurrent illnesses of varying severity, provide a sensitive index of the response to the infection. While an upper respiratory infection in a positive tuberculin reactor may produce slight alterations in the blood picture, it may at times evoke a leukocytic reaction similar to the acute forms of the disease already discussed. These changes, however, do not persist for any length of time, but when present serve as a useful guide in the management of the child's illness. It should be mentioned that the blood of a positive reactor during periods of inactivity may differ in no wise from that of the child who is not sensitive to tuberculin. During the height of a positive tuberculin reaction the peripheral blood usually shows a variable increase in neutrophilic leukocytes and monocytes, a decrease in lymphocytes and a higher M/L ratio.

The pathogenesis of the peculiar changes that take place in the lung adjacent to tracheobronchial nodes infected with tubercle bacilli, so prominent in this group, and which are reflected in the peripheral blood, may be explained in two ways: It may be related to the liberation of a toxin from the tissues injured by the tubercle bacillus or as a result of a chemical constituent of the organism itself. In the chemical analysis of this organism protein and phosphatid fractions have been isolated. Sabin and Doan<sup>16</sup> tested these substances biologically and found that the protein fraction produces a severely toxic state, marked febrile disturbances and an increase in the blood of the neutrophilic leukocytes. The lipid fraction, on the other hand, was nontoxic and was associated with a rise of monocytes and the development of epithelioid and Langhans giant cells. These cellular responses to the individual chemical fractions of the tubercle bacillus may account in part for different blood pictures that accompany the various clinical forms of tuberculosis.

In one-half of the cases of the latent group the eosinophils ranged from 7 to 14 per cent, values definitely above normal. The agents usually responsible for eosinophilia were eliminated, and the only common factor was sensitiveness to tuberculin. Since the eosinophilic leukocyte is usually linked with allergic states, the quantitative alterations in this type of cell might be considered to vary directly with the degree of allergic hypersensitivity. In the past sensitiveness to tuberculin has been regarded as coexistent with immunity. In the present series, in states of marked activity particularly in children whose illness was fatal, the fall in the number of eosinophils and often their complete disappearance occurred so frequently, that this change might be regarded as a sign of failing immunity. On the other hand, it cannot be stated from the results here reported that the stage of resistance is invari-

ably accompanied by an eosinophilic increase. The latter observation bears out in part the recent investigations of Rich,<sup>17</sup> who maintains that the terms "allergy" and "resistance" cannot be used interchangeably in tuberculosis.

According to the views of Sabin, the monocytes and their derivatives are the hosts for the tubercle bacillus. A persistently elevated monocyte count may, therefore, be construed as providing a ready vehicle for the dissemination of tuberculosis in the tissues. Experimentally, Doan and Sabin<sup>18</sup> have found that rabbits whose blood had a high preinfection M/L ratio manifested decreased resistance to the injection of bovine tubercle bacilli as contrasted with animals whose ratio was low. A problem worthy of investigation is to determine whether this high initial M/L ratio is present in races or families especially susceptible to tuberculosis. Studies are now in progress which have as their object the correlation of the immunity of the contact child with a negative tuberculin reaction and his blood picture. The results of this study will be included in the elaborated analysis of the cases of the present series which will appear in a later paper.

**Discussion.** From the data presented in this study, it is apparent that analysis of the complete blood picture serves a useful purpose in determining the status of the pathologic lesion in tuberculosis of infancy and childhood. While it is probably true that in human tuberculosis an increase in monocytes implies dissemination of the tubercle bacillus, it must be emphasized that the blood smear does not make the diagnosis of the disease. Increased monocytes have been found in a variety of nontuberculous conditions, although not at the high levels observed in the acute forms of tuberculosis. Epithelioid cells, more nearly specific for this disease, appear also in Hodgkin's disease.

Cognizance must be taken of the contention of Medlar,<sup>8</sup> that there is no unique leukocytic formula that is pathognomonic of tuberculosis. Every type of cell that responds at some stage to tissue injury by the tubercle bacillus is also called out in other inflammatory processes. When, however, the diagnosis has once been established differential counts taken periodically supply information which derives its value from the evidence now available of the rôle of each of the major white cells in the pathogenesis of the tuberculous lesion.

Confirmatory evidence has been obtained for the principle that regression and progression of the anatomic lesion are reflected in the circulating blood. These phases can be detected in the blood smear by identification of certain qualitative changes in the monocyte together with the individual fluctuations in the percentage and absolute numbers of this cell strain and of the polymorphonuclear neutrophil, eosinophil and lymphocyte. These determinations often afford the sole indication of changes in the course of the

infection and may antedate other diagnostic observations. In general, it may be stated that careful studies of the blood by the newer methods contribute materially in the complete investigation of all patients and are of particular value in studying the progress of the disease in tuberculous patients.

**Conclusions.** The blood picture of a tuberculous infant or child may be correlated with activity of the pathologic lesion in the tissues and organs.

The complete picture of activity in tuberculosis of infancy and childhood as manifested by the peripheral blood comprises the following: An increased white cell count, an elevation of polymorphonuclear neutrophils and monocytes, a drop in the number of eosinophils and lymphocytes and a rising monocyte to lymphocyte (M/L) ratio. Stimulated monocytes and less often epithelioid cells are usually observed in the supravital film only in the most acute cases. A reversion to a more normal blood picture is found in the stages of resistance and healing.

The trend of the disease may be ascertained from a numerical comparison of the different white cells determined periodically, with emphasis on the monocyte to lymphocyte ratio. Such an examination often furnishes the earliest indication of a change in the status of the disease in the young tuberculous patient.

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## THE PERCENTAGE OF EOSINOPHILS IN BLOOD SMEARS FROM INSULIN-TREATED DIABETICS.

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SINCE its inception in 1922 insulin has been found to give rise to several interesting and more or less important effects apart from its specific action upon carbohydrate metabolism. For instance, Lawrence and Buckley<sup>1</sup> discovered an eosinophilia in 10 out of 20 diabetics who were receiving insulin. Twelve diabetics who were not being so treated, with a single exception, did not show an abnormal number of eosinophils in blood smears. No strictly valid explanation could be offered to account for the occurrence of eosinophilia in the insulin-treated cases. The degree of eosinophilia bore no relation to the amount of insulin which the patients were receiving, although one insulin-resistant case reported by Lawrence,<sup>2</sup> on 200 units of insulin a day, provided the highest figures (12 to 20 per cent of eosinophils). This patient happened to be suffering from slight acne rosacea which, however, was discounted as a cause of the eosinophilia.

Whereas no factor other than the administration of insulin could be found to explain adequately the eosinophilia in the cases mentioned above, the authors have discussed the various possible ways in which this therapeutic agent might be responsible for the phenomenon. The physiologic action of insulin and the possibility of an allergic reaction were dismissed as being very improbable causes. The most likely explanation, according to the investigators, would seem to be irritation of the skin, occasioned by repeated subcutaneous injections of insulin. The eosinophilia found in insulin-treated diabetics would be analogous, therefore, to that frequently encountered in certain skin diseases.

The findings of Lawrence and Buckley suggest an added cause for eosinophilia as well as an interesting by-effect of insulin therapy.

In view of the fact that only a small series of observations were reported by them, and since no further contribution bearing upon the problem has been forthcoming, additional information may be opportune.

**Present Investigation.** The following study was made for the purpose of corroborating, if possible, the reports of Lawrence and Buckley and also to determine what changes, if any, occurred in the leukocytes in diabetes as disclosed by differential blood counts. Insofar as the eosinophils were concerned, it soon became apparent that eosinophilia was by no means such a commonly occurring incident in patients receiving insulin as the records of Lawrence and Buckley might indicate. Therefore, an answer to the question, "Does eosinophilia occur in insulin-treated diabetics?" was sought.

Seventy differential blood counts were carried out on 43 diabetic patients who were receiving insulin. As a control series, 22 counts were made on 20 diabetics who were not having insulin. The blood smears on which the counts were made were taken at different times of the day and at different seasons of the year. They were stained immediately after being obtained with a good quality Wright's stain. The technique included the use of buffered distilled water in diluting the stain and washing the smears, as suggested by the Feemsters.<sup>3</sup> All counts were made by the same observer. In the great majority of cases 500 white blood cells were counted; several portions of each smear thus were covered.

**Results.** The generally accepted normal range for eosinophils in blood smears is from 1 to 4 per cent of the leukocytes.<sup>4</sup> Nicholson<sup>5</sup> gives 2 to 5 per cent as representing the normal limits. The eosinophil percentages obtained in the insulin-treated group and in the noninsulin-treated group of patients are shown in Tables 1 and 2 respectively.

**Insulin-treated Cases.** This group includes patients with diabetes mellitus of various grades of severity who have been taking insulin from 1 to 4 times a day for periods of 1 day to 6 years. Of the 43 cases 9 showed percentages of eosinophils above 4. Of these 8 were above 5 per cent but only 1 above 8 per cent. As can be seen in Table 1, the majority of these cases provided figures which were but slightly above the normal. In only 1 case (No. 31) was frank eosinophilia present. Before starting the use of insulin, this patient showed 1 per cent of eosinophils in blood smears. Four weeks after taking 3 injections of insulin a day an eosinophilia of 12.6 per cent was discovered. One week later the count had gone up to 17.6 per cent, but after another week it had dropped to 10.8 per cent. This patient exhibited no local or general cutaneous reactions and responded well to the treatment. There was no apparent cause for the eosinophilia other than the use of insulin. Case 2 showed during the month of June an eosinophilia of 6.4 per

TABLE 1.—PERCENTAGE OF EOSINOPHILS IN INSULIN-TREATED DIABETICS.

Case No.	Age, yrs.	Sex.	Date.	Eosinophils, per cent.	Duration of insulin treatment.	Number of injections of insulin per day.	Units of insulin per day.
1	32	M	Junc 18, 1929	2.0	6 yrs.	3	70
			Jan. 8, 1930	1.6	6½ yrs.	3	55
2	18	F	Junc 19, 1929	6.4	2 yrs.	2	32
			Dec. 11, 1929	1.2	2½ yrs.	2	42
3	13	F	June 20, 1929	1.8	3 yrs.	3	48
			Dec. 27, 1929	1.8	3½ yrs.	3	45
4	16	F	Junc 22, 1929	3.4	2½ yrs.	2	45
			Jan. 10, 1930	2.4	3 yrs.	3	55
			Jan. 9, 1931	1.4	4 yrs.	3	46
5	60	F	June 25, 1929	1.0	3½ yrs.	2	15
			Jan. 4, 1930	1.8	4 yrs.	2	15
6	54	F	Junc 28, 1929	2.8	1 yr.	1	10
			Dec. 29, 1930	5.2	2½ yrs.	3	38
			Jan. 9, 1931	2.6	3½ yrs.	Q	0
7	12	F	Junc 26, 1929	1.6	2 mos.	3	35
			Dec. 13, 1929	3.8	8 mos.	3	50
8	48	M	Junc 29, 1929	1.2	4 yrs.	2	15
9	24	F	Dec. 8, 1929	0.4	6 mos.	2	25
10	25	M	Dec. 10, 1929	...	3 yrs.	3	70
			(10.30 A.M.)	1.4			
			( 4.00 P.M.)	3.2			
			Dec. 24, 1929	...	3 yrs.	3	80
			(10.00 A.M.)	4.0			
			(11.30 A.M.)	2.0			
			( 2.15 P.M.)	2.0			
			( 5.00 A.M.)	1.0			
11	5	F	Dec. 10, 1929	3.0	3 wks.	3	28
			Jan. 14, 1931	1.0	1 yr.	2	16
12	14	M	Dec. 11, 1929	2.8	3 yrs.	3	80
13	52	M	Dec. 12, 1929	5.6	6 mos.	3	35
			Jan. 15, 1931	4.4	1½ yrs.	3	60
14	40	F	Dec. 13, 1929	3.4	5½ yrs.	3	40
			Jan. 10, 1930	2.2	5½ yrs.	3	55
			Jan. 2, 1931	0.2	6½ yrs.	3	74
15	67	F	Dec. 13, 1929	2.2	1 yr.	2	45
			Jan. 6, 1931	1.6	2 yrs.	2	50
16	70	M	Dec. 17, 1929	1.0	5 yrs.	2	20
			Jan. 15, 1930	4.6	5 yrs.	2	20
17	60	F	Dec. 17, 1929	3.2	2 yrs.	3	45
			Dec. 26, 1929	...	2 yrs.	3	45
			(10.15 A.M.)	2.0			
			( 4.00 P.M.)	4.0			
18	50	M	Dec. 26, 1929	2.8	6 yrs.	2	35
19	49	M	Dec. 26, 1929	2.0	2½ yrs.	2	45
20	4	M	Dec. 27, 1929	1.4	1 yr.	2	8
21	50	F	Junc 21, 1929	6.8	0	0	0
			Dec. 30, 1929	8.0	6 mos.	2	8
			Jan. 25, 1931	5.0	1½ yrs.	2	18
22	50	F	Jan. 8, 1930	1.8	6 mos.	1	5
23	55	M	Jan. 9, 1930	1.4	3½ yrs.	2	22
24	14	F	Jan. 17, 1930	3.0	6 mos.	3	35
			Jan. 9, 1931	5.8	1½ yrs.	3	60
25	60	F	Dec. 16, 1930	0.8	2½ yrs.	3	40
26	22	M	Dec. 16, 1930	0	2 mos.	2	18
27	49	M	Dec. 16, 1930	0.4	0	0	0



TABLE 1.—PERCENTAGE OF EOSINOPHILS IN INSULIN-TREATED DIABETICS.  
(Continued.)

Case No.	Age, yrs.	Sex.	Date.	Eosinophils, per cent.	Duration of insulin treatment.	Number of injections of insulin per day.	Units of insulin per day.
28	68	F	Feb. 6, 1931	2.4	3 wks.	3	52
29	30	F	Dec. 19, 1930	2.4	1 mo.	2	22
30	62	F	Dec. 19, 1930	2.0	6 mos.	4	84
31	50	F	Dec. 21, 1930	1.0	5 days	2	18
			Dec. 29, 1930	1.0	0	0	0
			Jan. 30, 1931	12.6	4 wks.	3	38
			Feb. 6, 1931	17.6	5 wks.	3	38
			Feb. 13, 1931	10.8	6 wks.	3	42
32	52	M	Dec. 30, 1930	0.2	0	0	0
			Jan. 3, 1931	6.4	4 days	2	36
33	69	F	Jan. 6, 1931	3.8	1 day	2	20
			Jan. 30, 1931	4.2	3 wks.	2	36
34	17	M	Jan. 9, 1931	2.0	6 yrs.	3	64
35	42	F	Jan. 9, 1931	0.6	4 yrs.	3	30
36	65	F	Jan. 10, 1931	6.0	3 mos.	1	10
37	65	F	Jan. 10, 1931	1.4	3 wks.	1	15
38	65	F	Jan. 17, 1931	2.4	1 yr.	2	16
39	62	F	Jan. 20, 1931	0.8	6 wks.	3	42
40	12	M	Feb. 6, 1931	1.8	3 yrs.	3	58
41	13	M	June 21, 1929	5.4	0	0	0
			Dec. 28, 1929	1.8	0	0	0
			Jan. 31, 1931	3.2	1 yr.	2	46
42	60	F	Feb. 9, 1931	3.0	3 wks.	3	64
43	13	F	Feb. 18, 1931	3.6	1 mo.	2	24
Av.	..	..	....	3.0		(70 counts)	

TABLE 2.—PERCENTAGE OF EOSINOPHILS IN NONINSULIN-TREATED DIABETICS.

Case No.	Age, yrs.	Sex.	Date.	Eosinophils, per cent.
1	50	F	June 17, 1929	1.6
2	68	F	June 24, 1929	1.8
3	47	M	Dec. 13, 1929	2.0
4	79	M	Dec. 13, 1929	3.4
			Jan. 3, 1931	3.8
5	60	M	Dec. 17, 1929	6.4
6	55	F	Dec. 19, 1929	1.4
7	43	F	Dec. 21, 1929	0.8
8	30	M	Dec. 21, 1929	3.4
9	50	F	Jan. 1, 1930	10.6
10	37	F	Jan. 10, 1930	3.4
11	50	F	Jan. 10, 1930	3.6
12	70	F	Dec. 16, 1930	2.8
13	57	F	Dec. 19, 1930	4.4
14	75	M	Dec. 24, 1930	2.6
15	65	M	Oct. 1, 1930	1.0
			Jan. 5, 1931	2.0
16	68	M	Jan. 10, 1931	1.2
17	34	M	Jan. 29, 1931	0.2
18	65	F	Jan. 29, 1931	1.2
19	60	M	Feb. 5, 1931	3.0
20	51	F	Feb. 5, 1931	4.6

Average (22 counts) . . . . . 2.9

cent. At that time the patient was in the midst of one of her annual "hayfever" attacks. Six months later, when no "hayfever" symptoms existed, there was 1.2 per cent of eosinophils. Case 21 showed an eosinophilia of 8 per cent 6 months after taking 2 injections of insulin per day and 5 per cent after another year of similar treatment. But this patient had 6.8 per cent of eosinophils in her blood while under treatment by diet alone before commencing the use of insulin. Cases 17 and 33 had marked skin reactions, due to the insulin injections, yet no eosinophilia was observed. Comparison of the eosinophil percentages before with those obtained after the commencement of the use of insulin in Cases 27, 32 and 33 shows that a slight increase did occur. However, in none of these was the increment great enough to place them within the scope of definite eosinophilia. The fact that fluctuations in the eosinophil percentages occur from time to time during the day, as exemplified in Case 10, must be taken into account when interpreting the significance of these slight increases. The average for the whole group was 3 per cent of eosinophils. Apart from the one high case, the range was from 0 to 8 per cent.

**Noninsulin-treated Cases.** Twenty-two differential blood counts on 22 diabetics who were being treated by diet alone without insulin, disclosed results (Table 2) which did not differ appreciably from those obtained in the insulin-treated group. Two cases showed eosinophil percentages of 6.4 and 10.6, for which no explanation was discovered. The remaining 18 cases gave figures between 0.2 and 4.4 per cent. The average for the group was 2.9 per cent.

**Discussion.** While eosinophilia may result from repeated injections of insulin, it is by no means a commonly occurring incident, at least under the conditions of the present investigation. Only one patient was followed with any degree of regularity following the commencement of insulin therapy. It is possible that eosinophilia may have been temporarily present in others of this series but not discovered by a single blood examination or by counts made at long intervals after beginning the use of insulin. The investigation is being continued, however, with these points in mind. No attempt is made to explain the discrepancy in the results obtained by Lawrence and Buckley and those recorded here. To ascribe the lack of agreement to any such factors as differences in insulin dosages, brand of insulin, locality or climatic conditions would be mere speculation. It is of interest to note, in this regard, that Lawrence and Buckley observed an increase in the eosinophilia in several cases during the very hot weather of the summer months, the counts being lower before and after that time.

Reference to eosinophilia ordinarily recalls the association of this phenomenon with allergic and anaphylactic states, certain skin lesions and protozoal infestations. The medical literature of the

past several years supplies instances of reactions to insulin which are unrelated to changes in the blood-sugar concentration and apparently independent of any hormone activity. Such reactions may be local or general in character. They may be limited to the region surrounding the site of injection, and consist of erythema with varying degrees of localized induration and swelling. More serious types of reaction may occur, manifesting themselves by generalized urticaria and edema or by gastrointestinal symptoms, as in a case reported recently by Williams.<sup>6</sup> Reactions such as those referred to above were not infrequent apparently during the early days of insulin usage. They could be attributed in all probability to protein contained in the original insulin preparations. Improved methods of purification and concentration soon obviated these untoward effects to a large extent.

That a specific hypersensitiveness to insulin *per se* may exist is suggested by the immunologic studies of Tuft.<sup>7</sup> This particular type of hypersensitiveness is probably analogous to the so-called drug idiosyncrasies. Another variety of hypersensitiveness also can occur in spite of adequate purification and concentration of insulin and is evidently dependent upon some factor contributed by the source of supply of the product. For example, a patient may be intolerant to insulin derived from the pancreas of the pig, yet experience no ill effects from insulin prepared from beef pancreas, as in the case described by Williams.<sup>6</sup> No eosinophilia was noted in this case, however. A similar example of insulin intolerance is mentioned by Tuft.<sup>7</sup> The case of a patient who exhibited local reactions to insulin at the commencement of treatment, with the subsequent disappearance of the reactions, is reported by Lasersohn.<sup>8</sup> No mention is made regarding the blood counts by the two latter observers.

In view of these data alone, the occurrence of eosinophilia during insulin therapy is by no means an improbability. If it does occur, its cause will possibly be found in some more subtle influence than mere repeated punctures of the skin by the hypodermic needle. In the meantime the question, "Does eosinophilia occur in insulin-treated diabetics, and if so, why?" is wanting an answer.

**Summary.** Eosinophilia is not a generally occurring incident in diabetics receiving insulin treatment. Its presence in some cases must be admitted. Seventy differential blood counts from 43 diabetics receiving insulin revealed a definite eosinophilia in only 1 case. This low incidence of eosinophilia under such conditions is not in accord with the findings of previous investigators. No explanation is offered for the discrepancy in the results. The average percentage of eosinophils in 43 diabetics receiving insulin was not appreciably different from the average percentage of eosinophils in 20 diabetics who were treated by diet alone without insulin.

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**FURTHER STUDIES IN A CASE OF CALCIFICATION OF  
SUBCUTANEOUS TISSUE ("CALCINOSIS UNIVERSALIS")  
IN A CHILD.\***

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In 1926 Wilens and Derby<sup>1</sup> reported a case of "calcinosis universalis" seen at the Children's Hospital, Boston. Recently we have had the opportunity of observing this same patient for a prolonged period in the research ward of the Massachusetts General Hospital. It was hoped that a more detailed study of this patient might throw further light on the underlying cause of this obscure condition. Accordingly, we undertook a study of the calcium, phosphorus and nitrogen metabolism in conjunction with chemical and histologic examinations of biopsied material.

**Case Report.** B. R. C., M. G. H. No. 300059, a white American school-boy, aged 10.5 years, was admitted to the metabolism ward of the Massachusetts General Hospital on April 2, 1930.

A study of the *family history* revealed no known tendency to chronic disease. No relatives had been known to have a condition similar to that of the patient.

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The *past history* showed that the child's birth (on November 27, 1919) had been normal, that he was breast fed for 2 months and then was given Mellin's food. He gained normally. His first tooth was acquired when 9 months of age, and he walked at about 18 months. At the age of 2 years he had pertussis and four convulsions of unknown etiology; at 3 years he had bronchopneumonia; at 4 years, lobar pneumonia; at 5 years, measles and scarlet fever; at 7 years, mumps; at 9 years, septic sore throat.

The *present illness* began about 8 years ago, when the patient was between 2 and 3 years of age. At this time his mother noticed that his legs appeared weak and that he dropped to his knees when attempting to walk. About 7.5 years ago several small painless swellings appeared on the crest of both tibiae. Later similar hard swellings appeared under the skin in various places over the body. Six years ago, apparently for the first time, it was noticed that calcareous material was extruded from the swellings over the left tibia. About 4 months after this occurrence one of the swollen areas began to discharge puriform liquid along with chalky material.

Five and a half years ago he was admitted to the Children's Hospital because of acute swelling and tenderness in the region of the left knee. At that time the serum calcium and phosphorus were found to be normal. The subcutaneous nodules were examined histologically. Chemical analysis revealed the presence of calcium salts. These findings have been reported.<sup>1</sup>

One and a half years ago he was again admitted to the Children's Hospital because of acute pain and swelling in the region of the right elbow. A note made at that time stated that since his first admission there had been no important change in his condition.

Nine months ago (July 7, 1929) he was admitted to the Massachusetts General Hospital on the surgical service. At that time the abscesses in the skin and subcutaneous tissue over the left elbow were incised and drained. Three months later he was again admitted to the surgical service of the Massachusetts General Hospital because of abscesses about calcareous nodules over the left elbow and both knees.

In the weeks just preceding the hospital admission with which this present paper is concerned the patient had continued about as before. New calcareous nodules had formed in various places over the body, older ones had been extruded through the skin from time to time. On several occasions particularly abundant accumulations of the chalky material in the tense soft tissue covering joints had given rise to acute pain and swelling. Where partly extruded nodules had become secondarily infected superficial abscesses had formed and pus had been discharged along with the calcareous material.

*Physical examination* in the ward showed a poorly developed and poorly nourished boy. He looked chronically ill. His facial expression and speech were those of an older individual. His teeth were poor; those in front, particularly above, showed notched margins and serrations across them about midway from gum to free border. The tonsils were moderately enlarged and scarred. No glands were felt except for several swollen, discrete, nontender nodes along the anterior border of the sternocleidomastoid muscle on each side. Many hard subcutaneous nodules were present in various places. These nodules were composed of white or yellowish-white chalky material. Their size varied from the smallest possible up to 1 cm. or more in diameter. In several areas two or more fairly large nodules had coalesced to form a much larger accumulation of calcareous material. The nodules were most numerous on the extremities, particularly about the knees, elbows and anterior aspect of the legs. It is worthy of note that these lesions were entirely absent over the scalp, thorax and abdomen. There were lesions in all stages of development from nodules completely covered by intact skin to those just breaking through

and extruding the chalky material (with open, shallow ulcerations in some places) to the final scars. Small superficial ulcers in various stages of breaking down and healing were present over both knees, the left foot, the buttocks and both elbows. None of the joints were swollen, red, hot or tender. Some were partly ankylosed because of the extensive accumulation of calcareous material about them. The right thigh could be flexed only to make an angle of about 90 degrees with the trunk. Motion at the right knee was limited. The lower leg could be flexed to make a 90-degree angle with the thigh and could be extended to within 35 degrees of full extension. Because of this partial ankylosis of the right knee joint, the boy walked with a limp. The right arm could be abducted about 45 degrees. Motion was limited at both elbows. Complete extension of the right arm was lacking by 15 degrees; flexion was but slightly limited. Extension of the left arm was normal, but flexion was limited about 30 degrees.

*Laboratory Data.* The urine was normal except for the presence of a slight trace of albumin. On admission his erythrocyte count was 4,500,000; leukocyte count, 8250 and hemoglobin (Tallquist) 65 per cent. The blood smear was normal, except for a 7 per cent eosinophilia. Two months later the erythrocyte count was 5,000,000; leukocyte count, 10,100; hemoglobin (Tallqvist), 80 per cent, and the blood smear was normal. A blood Hinton test was negative. The blood sugar was 105 mg. (fasting); nonprotein, nitrogen 30 mg., and uric acid, 1.2 mg. per 100 cc. The blood cholesterol was 120 mg. per 100 cc. The carbon dioxid combining power of the blood was normal (57.1 vols. per cent). The blood serum calcium and phosphorus were always found to be normal. The basal metabolic rate was on one occasion +16 as predicted on height and +34 as predicted on weight (Talbot special standard).

*Roentgen Ray Report.* The following interpretation of the roentgenograms was submitted by Dr. A. O. Hampton: "Examination included anteroposterior and lateral views of the entire skeleton. An effort was made to show both the soft tissues and the bone structure. Calcium deposits were diffusely scattered in the subcutaneous tissues of the arms, legs, buttocks and axillæ. The scalp, neck and chest were essentially normal. The calcium deposits were most pronounced in the right arm and right thigh. Of the joints, the tissues of the knees and elbows showed the greatest deposits of calcium. The shape and size of the calcium deposits varied from 1 mm. to 3 cm. in diameter, except in the region of the right sartorius muscle, the right hamstring muscles and the extensors of the left wrist. In these regions deposits extended nearly the whole length of the muscles and produced a calcium cast of the muscles mentioned. The calcium deposits showed no bone structure, being composed of multiple small irregular granules grouped rather compactly in the larger deposits and appearing fairly discrete in the smaller areas. The joint spaces were preserved and the joint outlines appeared smooth. There was no definite evidence of calcium deposits within any of the joint cavities. The knees showed an unusually dense accumulation of calcium very near or partially surrounding the joint capsule. All of the bones were rather small, thin and the bone trabeculæ were coarse and slightly separated. The cortex of the bones was unusually thin and the medullary canals were preserved. The epiphyses showed no abnormality in time of fusion. The epiphyseal lines were smooth and not so dense as usual. There were no fractures or deformities of any of the bones."

*Course in the Hospital.* During his stay of 3 months in the ward no essential change was noted in his condition. He was up and about practically all the time except for a day or two following the biopsies. Three times during the 3 months his temperature rose to 100° or above; there were also a few other transient temperature rises to less than 100°. These

periods of fever were associated with acute swelling and tenderness about one or more of the nodules. The biopsy wounds healed promptly. Orthopedic consultants thought that operative interference with his ankylosed joints was inadvisable. He was discharged unrelieved on July 3, 1930.

I. **Studies of Biopsy Material.** On April 28, under local anesthesia, a subcutaneous nodule was removed from each thigh by Dr. V. P. Williams. A portion of this material was preserved for histologic study and the rest used for chemical analysis.

**Chemical Studies. Methods Used.** 1. **Uric Acid.**<sup>2</sup> 180 mg. of the wet samples were transferred to a 25-cc. volumetric flask. To this were added 5 cc. of 10 per cent sodium tungstate and 5 cc. of two-thirds normal sulphuric acid. The total volume was then made up to 25 cc., the flask shaken and the contents poured on to a filter. Uric acid was determined on the filtrate according to the method of Benedict.<sup>3</sup>

2. **CHOLESTEROL AND FATTY ACIDS.**<sup>\*</sup> 3.0623 gm. of wet sample were extracted continuously for 36 hours in a Soxhlet apparatus (with alcohol for 24 hours and with ether for 12 hours). After extraction the dried residue was found to weigh 1.5373 gm. Cholesterol and fatty acid were determined on the combined alcohol and ether extracts according to the method of Bloor.<sup>4</sup>

3. **CALCIUM AND PHOSPHORUS.** One-tenth gm. of the above dried material was weighed into an evaporating dish. This was ashed over a free flame and finally in an electric muffle furnace. The ash was dissolved in a few cubic centimeters of 50 per cent hydrochloric acid and the volume was made up to 100 cc. In this solution calcium was determined by the method of Fiske<sup>5</sup> and the phosphorus by that of Fiske and Subbarow.<sup>6</sup>

4. **CARBON DIOXID.**<sup>†</sup> This was determined on the dried material by the method outlined by Shear and Kramer.<sup>7</sup>

The following values were obtained:

	Wet material, gm. per 100 gm.	Dry material, gm. per 100 gm.
Water . . . . .	49.80	
Uric acid . . . . .	.00417	
Cholesterol . . . . .	.415	
Fatty acid . . . . .	1.061	
Calcium . . . . .	..	27.60
Phosphorus . . . . .	..	12.75
Carbon dioxid . . . . .	..	4.09

The above figures show a low uric acid content. The value is higher than that obtained by Folin, *et al.*,<sup>2</sup> for the muscle of normal dogs (1.2 to 2.5 mg. per 100 gm.) and normal rabbits (1.2 to 1.4 mg. per 100 gm.), but it is certainly low enough to preclude any possibility that the concretions were composed of urates.

Because of the lack of comparable data in the literature, we are unable to properly interpret the values obtained for cholesterol and fatty acids. However, they are no greater than one might expect with the amount of normal tissue breakdown involved in pathologic calcification.

The values obtained for calcium and phosphorus are quite in accord with those reported for pathologic calcification by previous

\* We are greatly indebted to Dr. E. R. Lenherr, of the New England Deaconess Hospital Laboratory, for the cholesterol and fatty acid determinations.

† We wish to thank Dr. L. T. Fairhall for the determination of carbon dioxid.

workers. Gascard,<sup>8</sup> in 1900, in a brief note gave the results of an analysis of hard subcutaneous tumors removed at autopsy from the inner side of the thigh of a young man. Harlay,<sup>9</sup> in 1903, analyzed a portion of a subcutaneous calcareous mass removed from the outer aspect of the right knee of a woman, aged 60 years, with arthritis. After recalculation to provide uniformity these results may be compared with our own as follows:

	Gascard. Per cent.	Harlay. Per cent.	Authors'. Per cent.
Calcium . . . . .	30.00	31.82	27.60
Phosphorus . . . . .	13.50	13.04	12.75

In our case if one subtracts the calcium in the form of calcium carbonate from the total calcium content one obtains a calcium to phosphorus ratio quite similar to that found in normal bone. The residual calcium to phosphorus ratio can be calculated according to the formula used by Shear and Kramer.<sup>7</sup> This formula is as follows:

$$\frac{\text{Residual Ca}}{\text{Residual P}} = \frac{\text{Total Ca} - \text{Ca carbonate}}{\text{Total inorganic P}}$$

$$4.09 \times 0.91 = 3.70 \text{ gm. calcium present as CaCO}_3$$

$$\frac{\text{Residual Ca}}{\text{P}} = \frac{27.6 - 3.72}{12.75} = 1.87$$

This value (1.87) compares favorably with the theoretical calcium to phosphorus value of 1.94 for  $\text{Ca}_3(\text{PO}_4)_2$  of normal bone and with the values (1.88 to 2.01) obtained by Kramer and Shear<sup>10</sup> for pathological calcifications in man.

**Histologic Study.** The specimen consisted of a number of irregular pieces of skin and subcutaneous tissue. The subcutaneous tissue contained a number of relatively large irregular deposits of an amorphous, white chalk-like material. This material was solid in certain areas, in others it had the consistency of a thick paste.

**Microscopic Examination.** Paraffin and frozen sections, formaldehyd and Zenker's fixation stains: Hematoxylin and eosin, eosin methylene blue, Klotz' and von Kossa's silver nitrate methods of staining calcium.

Most of the epidermis was thrown into irregular folds. The papillary layer of the epithelium was very irregular, and superficial desquamation of the horny layer was more prominent than normal. In some areas the corium was very dense in structure, although the coil glands and hair follicles distributed throughout this layer appeared normal. In most fields the corium was free of calcareous deposits, although in a few the deposition of calcium had encroached upon the basal layer of the corium. In such fields the fibrous tissue surrounding the calcified masses was intimately fused with the corium.

Several microscopic sections included cross sections of entire calcified subcutaneous nodules. These areas were usually found beneath the corium in the subcutaneous fat. They were filled with irregular masses of varying sizes which stained intensely basic. This material was seen as small, finely divided particles, having a granular appearance, or as larger particles



which were globular or angular shaped. In the preparations stained by the methods of von Kossa and Klotz for the identification of calcium these granular, globular and crystalline masses were stained black. Preparations stained by the method of Klotz for demonstrating calcium in the form of of both phosphate and carbonate showed a positive reaction in a greater part of the deposit than did von Kossa's method of staining calcium phosphate.

In the preparations stained with hematoxylin and eosin and the eosin methylene blue each area of calcification was surrounded by areas of fibrosis. Depending apparently on the age of the calcium deposit, this layer of fibrosis varied from one of dense cellular collagen to one of fibroblastic proliferation and bloodvessel ingrowth. In almost all portions of the sections numerous, irregular giant cells of the foreign-body type could be found about the margins of the calcified masses. No cholesterol crystal clefts were found in any of the calcified areas or within any of the giant cells. Many of the foreign-body giant cells had formed about calcareous particles. Occasional vacuolated endothelial leukocytes (foam cells) were present about the margins of the calcified areas. No bone formation was seen.

The sequence of the pathologic changes leading to the large areas of calcification remained obscure after histologic study. The impression was gained, however, that the initial lesions were represented by those areas in which whole or partial fat lobules were altered by deep basic staining granules. In the least involved areas these granules were seen only around the periphery and in between intact fat cells. (Fig. 9.) Where a more pronounced calcareous deposition had occurred the entire fat cells were granular and stained by basic dye. Other fat cells were entirely obscured by the dense lime deposit. The absence of any evidence of antecedent fat necrosis was a noteworthy feature. A few fields showed a scattering of lymphocytes and polymorphonuclear leukocytes. In areas where the altered fat cells were still recognizable, surrounding fibroblastic proliferation was scant in amount and little collagen had been laid down.

Occasional bloodvessels near the calcified areas showed thickened walls in which hyalinization of the medial coat had occurred. Perivascular infiltration with lymphocytes was noted about a few of the bloodvessels. (Fig. 10.)

Except for the findings of more numerous peripheral giant cells and more complete encapsulation with fibrous tissue, these calcareous lesions showed no important differences from those seen in the sections made in 1926, which we have had the opportunity of studying.

TABLE 1.—DIET AND THERAPY USED DURING METABOLIC STUDIES.

Three-day period.	Type of diet.		Therapy.	
	Calcium.	Phosphorus.	Ammonium chlorid, gm. per day.	Irradiated ergosterol,† mg. per day.
1 to 7 . . .	Very low	Mod. low*	None	None.
8 to 13 . . .	Very low	Mod. low	4†	None.
14 to 16 . . .	Very low	Mod. low	6	15
17 to 18 . . .	Very low	Mod. low	6	None.
19 to 20 . . .	Very low	Mod. low	None	None.
21 to 23 . . .	Mod. low*	Very low	None	None.
24 to 26 . . .	Mod. low	Very low	6	None.
27 to 28 . . .	Mod. low	Very low	None	None.

\* Inadequate for a normal child of the patient's age. For actual figures see Table 2.

† For 2 days of Period 12 and during Period 13, 6 gm. a day were given.

‡ Kindly supplied by the Winthrop Chemical Company of New York City.

TABLE 2.—MASTER B. R. C. (AGED 10 YEARS).  
(All values are expressed as Average Figures per Three-day Period.)

Periods.	Dates, 1930.	Average weight, kg.	Phosphorus.				Calcium.				Nitrogen.				Diet.				Blood serum.				Therapy, NH <sub>4</sub> Cl, gm. per day.			
			Output.			Balance.	Output.			Intake.	Balance.	Output.			Intake.	Balance.	CHO.	Protein.	Fat.	Calories.	Fluid.	Date.		CO <sub>2</sub> .	Ca.	P.
			Urine.	Feces.	Total.		Urine.	Feces.	Total.			Urine.	Feces.	Total.												
1-7.	4/3-4/24	24.2	1.054	.316	1.400	+427	.050	.046	.096	.266	+170	19.2	2.3	21.5	26.2	+4.7	608.1	163.5	156.4	4786	3600	4/24	57.1	10.2	5.8	
8-13	4/24-5/12	24.3	1.465	.321	1.786	+027	.429	.017	.476	.264	-212	25.9	2.2	28.1	26.1	-2.0	598.9	162.7	158.9	4799	3783	5/2 5/9	51.8 51.2	9.9 10.3	5.7 6.2	
14-16	5/12-5/21	24.0	1.000	.309	1.399	+428	.403	.034	.437	.267	-170	20.3	2.4	22.7	26.2	+3.5	711.6	163.5	159.0	4932	3900	5/13 5/17	48.8 53.9	10.0 9.5	5.1 5.4	6†
17-18	5/21-5/27	23.8	1.876	.262	2.138	-311	.963	.027	.990	.267	-773	31.0	2.6	33.6	26.2	-7.4	691.6	163.5	159.0	4738	3900	5/22	49.0	9.8	5.6	6
19-20	5/27-6/2	24.1	1.377	.287	1.664	+163	.237	.038	.275	.267	-008	21.3	2.6	23.9	26.2	+2.3	651.6	163.5	159.0	4626	3900	5/27	52.4	8.8	5.3	
21-23	6/2-6/11	24.1	1.466	.200	1.666	-556	.186	.043	.229	.666	+437	20.9	2.5	23.4	24.9	+1.5	711.6	155.7	110.4	4902	3900	6/4	53.4	9.8	6.1	
24-26	6/11-6/20	24.3	1.423	.191	1.614	-547	.695	.045	.740	.645	-095	21.1	2.4	23.5	24.3	+0.8	713.6	151.6	116.4	4754	3900	6/19	46.3	....	..	6
27-28	6/20-6/26	23.9	0.957	.220	1.177	-216	.228	.031	.259	.599	+340	14.1	2.2	16.3	21.7	+5.4	707.2	135.6	102.0	4289	3750	6/23 6/24	48.4 ...	9.9	5.6	

\* For two days of Period 12, and during Period 13, 6 gm. a day were given.

† Also 15 mg. ergosterol per day.

II. Studies of Calcium, Phosphorus and Nitrogen Metabolism. *Methods.* The methods used in the metabolism ward have been outlined in a previous paper.<sup>11</sup> All diets were carefully calculated and weighed, fluids carefully measured and excreta saved in 3-day periods. Determinations of calcium were done according to the method of Fiske;<sup>5</sup> phosphorus, that of Fiske and Subbarow;<sup>6</sup> carbon dioxide combining power, that of Van Slyke;<sup>12</sup> total nitrogen, the Kjeldahl method.<sup>13</sup> These studies were carried out for 12 weeks. This enabled us to detect whether or not there was any gross deviation from the values obtained in a study of normal individuals under similar conditions.<sup>14</sup> It also allowed us to note the effect of dietary changes and various forms of therapy. The table below briefly outlines the various conditions under which the patient was studied. One should note the divisions of this study and the number of periods included in each division.

In Table 2 the metabolism data are presented. It will be observed that the values are expressed as the average of all the periods that comprise that particular division of the study. It will be seen that during the control periods, 1 to 7 (21 days), on an inadequate calcium intake (0.266 gm. per 3-day period), the urinary calcium was 0.050 gm. and the fecal calcium was 0.046 gm., making a total output of 0.096 gm. with a resulting *positive* calcium balance of +0.170 gm. per 3-day period. These values are definitely abnormal as compared with those obtained from normal adult individuals studied on a similar diet. In their series of 13 normal adult subjects Bauer, Albright and Aub<sup>14</sup> found the average calcium excretion on the same low calcium diet to be 0.79 gm. (urinary 0.6 gm. plus fecal 0.19 gm. per 3-day period), resulting in a *negative* calcium balance of 0.46 gm. These figures were obtained on adults, to be sure, but in 2 essentially normal boys, aged 9 and 14 years, we obtained the following results while using this same low calcium diet:

TABLE 3. — AVERAGE VALUES PER 3-DAY PERIOD ON TWO APPARENTLY NORMAL BOYS.

	Case 1. 14	Case 2. 9
Age, yrs. . . . .		
Calcium:		
Urine . . . . .	0.181	0.176
Stool . . . . .	0.290	0.225
Total output . . . . .	0.471	0.401
Intake . . . . .	0.240	0.280
Balance . . . . .	-0.231	-0.121
Phosphorus:		
Urine . . . . .	2.175	1.100
Stool . . . . .	0.434	0.460
Total output . . . . .	2.609	1.560
Intake . . . . .	2.667	1.910
Balance . . . . .	+0.058	+0.350
Number of 3-day periods averaged . . . . .	3	6

Thus one notes that in the case under discussion both the urinary and fecal calcium excretions were definitely lower than in either of the two apparently normal boys studied. These excretions were sufficiently low to enable the patient to maintain a *positive calcium balance* in spite of the *extremely low-calcium intake*. He excreted approximately 0.4 gm. less calcium per 3-day period than did Case 1 and approximately 0.3 gm. less than Case 2. The low fecal and urinary calcium excretions indicate that there may have been increased absorption and that there was increased retention. If the calcium absorbed had not been retained the urinary calcium value would have exceeded the value observed in normal individuals. Actually, there occurred an accompanying decrease in the urinary

calcium excretion. This finding further emphasizes the ability of the tissues of this patient's body to retain calcium.

This same bodily retention is evident in the case of phosphorus. The 3-day intake was only 1.826 gm., the urinary excretion was 1.054 gm., the fecal excretion, 0.346 gm., and the resulting balance, a positive one to the extent of 0.427 gm. per 3-day period. The phosphorus balances for Cases 1 and 2 were +0.058 gm. and +0.350 gm. respectively. (Table 3.)

The average values for Periods 8 to 13 (18 days), during which ammonium chlorid was given, show that the urinary calcium was increased more than eight times that obtained in the control periods, so that the final calcium balance was -0.212 gm. per 3-day period. Phosphorus shared in this increased excretion with the production of a final balance of +0.027 gm. per 3-day period as contrasted with the control value of +0.427. In the case of both calcium and phosphorus this larger output was entirely urinary. The fecal calcium was essentially the same during the medication periods as in the control periods. The fecal phosphorus was slightly less during the medication period. Thus the administration of ammonium chlorid resulted in the mobilization of calcium and phosphorus in a manner similar to that seen in other individuals.<sup>15</sup>

During Periods 14 to 16 (9 days) the low calcium diet and ammonium chlorid were continued, but in addition 15 mg. of irradiated ergosterol were administered daily by mouth. During the administration of irradiated ergosterol the fecal calcium fell from 0.047 to 0.034 gm. The urinary calcium was reduced from 0.429 to 0.403 gm. These changes resulted in a reduction of the negative calcium balance from -0.212 to -0.170 gm. The fecal and urinary phosphorus were likewise diminished. The former decreased from 0.321 to 0.309 gm., the latter from 1.465 to 1.090 gm. The positive phosphorus balance increased from +0.027 to +0.428 gm. We have observed<sup>16</sup> a similar decrease in the fecal calcium and phosphorus accompanied by a diminution of the urinary calcium and phosphorus when irradiated ergosterol was administered to individuals with calcium deficiency diseases. In the present case the fecal excretions of calcium and phosphorus were only slightly influenced. The effect on the urinary excretions was more pronounced in the case of the phosphorus. Failure to obtain a greater decrease in the fecal excretions may have been due to the fact that the fecal values were abnormally low before irradiated ergosterol therapy was instituted. This unusual finding is seemingly a manifestation of the disease under discussion. The irradiated ergosterol effect is best interpreted as an increased retention of both elements. Therefore, irradiated ergosterol administration in this instance accentuated the already existing abnormality of calcium metabolism, namely, increased absorption from the intestinal tract and increased retention.

During the next two periods, 17 and 18, all conditions were the same except that irradiated ergosterol was omitted. During these 6 days was obtained the greatest excretion of calcium and phosphorus observed at any time during the course of the investigation. This added output of calcium and phosphorus was entirely urinary. The value for urinary calcium rose from 0.403 gm. per 3-day period in the previous periods to 0.963 gm. per 3-day period during Periods 17 and 18. The corresponding phosphorus value rose from 1.090 to 1.876 gm. On the other hand, the values for fecal calcium and phosphorus fell, in the case of the former from 0.034 to 0.027 gm. and of the latter from 0.309 to 0.262 gm. per 3-day period. The total calcium balance became -0.723 gm. per 3-day period and that of the phosphorus -0.311 gm. per 3-day period.

This marked increase in calcium and phosphorus excretion following the discontinuance of irradiated ergosterol is difficult to interpret. The increased excretion of these elements was in excess of that retained as a

result of ergosterol administration. This observation indicates that the effect of irradiated ergosterol was more pronounced in Periods 14 to 16 than was suspected from the comparison of the data obtained during these periods with those obtained during Periods 8 to 13.

The low average value of 0.027 gm. of calcium in the feces during Periods 17 and 18 may be taken to indicate a continuance of the ergosterol effect. The same thing may be stated regarding the corresponding values for phosphorus. This becomes evident when the values are tabulated, period by period.

TABLE 4.—TOTAL CALCIUM AND PHOSPHORUS BALANCE.

	Period 16.	Period 17.	Period 18.	Period 19.
Calcium:				
Urine . . . . .	0.432	0.940	0.985	0.316
Feces . . . . .	0.034	0.023	0.031	0.049
Total output . . . .	0.466	0.963	1.016	0.365
Intake . . . . .	0.267	0.267	0.267	0.267
Balance . . . . .	+0.199	+0.696	+0.745	+0.098
Phosphorus:				
Urine . . . . .	1.079	1.936	1.815	1.464
Feces . . . . .	0.320	0.235	0.289	0.318
Total output . . . .	1.399	2.171	2.104	1.782
Intake . . . . .	1.827	1.827	1.827	1.827
Balance . . . . .	+0.426	+0.344	+0.277	+0.450

Here it will be seen that although the fecal excretion of calcium was only 0.023 gm. during Period 17, it rose to 0.031 gm. in Period 18 and to 0.049 gm. in Period 19.

Periods 19 and 20 were control periods during which no medication was given. No comment is necessary other than to point out a tendency to return to the state which existed in the original control periods, 1 to 7.

During Periods 21 to 28 the diet employed was higher in calcium content and lower in phosphorus. This dietary change was made in order to determine whether or not less calcium would be retained if less phosphorus was given. One notes that during the first three periods on this diet the calcium balance was positive to the extent of +0.437 gm. and the phosphorus balance became negative (−0.556 gm.). Thus it will be seen that the additional calcium in the diet was entirely absorbed and retained. The resulting negative phosphorus balance was probably due to an inadequate phosphorus intake. *From these findings it is apparent that this individual was capable of retaining calcium other than in combination with phosphorus.*

The administration of ammonium chlorid in Periods 24 to 26 resulted in an increased calcium excretion, but was without effect on the phosphorus excretion. The calcium metabolism data suggest that *the ammonium chlorid acidosis prevented the retention of calcium and also mobilized calcium from the tissues (which had been retained previously) in some form other than calcium phosphate.* We are unable to state what this combination may have been. The failure to obtain an increase in the phosphorus excretion suggested that the ammonium chlorid therapy had been without effect on the phosphorus metabolism. However, the discontinuance of the drug during Periods 27 and 28 resulted in a marked diminution in the urinary phosphorus.

With the discontinuance of ammonium chlorid, in Periods 27 and 28 there resulted a return to the normal state for the dietary régime employed.

The nitrogen metabolism (Table 2) did not show noteworthy changes at any time. Except for Periods 8 to 13, during which the balance was −2.0 gm. per 3-day period, and Periods 17 to 18, during which it was −7.4 gm., all balances were positive, ranging from +0.8 to +5.4 gm. per 3-day period. The increased negative balance in Periods 17 to 18 probably explains some of the increased output of phosphorus during these periods.

It is noteworthy that throughout the period of study the patient did not appreciably lose weight. (Table 2.)

In Table 2 will be found the values for blood serum calcium and phosphorus. Throughout the period of study all values for calcium and phosphorus were normal except for the calcium value of 8.8 mg. per 100 cc. of serum on May 27, which coincides with the great loss of calcium from the body occurring at this time (Period 18). During the administration of irradiated ergosterol the serum calcium was unchanged; the serum phosphorus fell slightly and rose again after its discontinuance.

The acidosis obtained by ammonium chlorid was judged by determinations of the carbon dioxid combining power of the blood. At no determination was this found to be below 46.3 vols. per cent (on June 19).

**Discussion.** The occurrence of calcareous nodules in the subcutaneous tissues ("calcinosis universalis") is a rare condition affecting particularly children. Cases occurring in children have been reported by Langmead,<sup>17</sup> Versc,<sup>18</sup> Tisdall and Erb,<sup>19</sup> Morse<sup>20</sup> and Duret.<sup>21</sup> The last-named author observed the disease in a sister and brother. We have found no other reference in the literature which would suggest a familial tendency. The question of the etiology of the disorder has been discussed by each writer, but has remained unsolved. In the following summary, the results of the present study have been analyzed.

The possibility that this condition might be a disorder of uric acid metabolism seems unlikely because of the normal blood value and the negligible quantity of uric acid found in the biopsy specimen.

There is very little to point to a gross disturbance of cholesterol or fat metabolism. The blood cholesterol was normal. The cholesterol and fatty acid content of the biopsied specimen was not more than one might expect.

Further analysis of the calcareous material showed it to be composed of calcium carbonate and calcium phosphate in proportions essentially the same as that of normal bone and pathologic calcifications found elsewhere.

Our histologic study was limited to the subcutaneous nodules easily accessible for biopsy. This examination did not reveal any adequate explanation of the calcifying process. There was no evidence of any of the usual abnormalities which are known to cause pathologic calcification, namely: chronic inflammation, infarction, hemorrhage or tissue necrosis. The earliest abnormality noted was the deposition of finely divided calcium particles around the periphery of fat cells, which otherwise histologically appeared to be normal. No evidence of "calcium binding substances within degenerated areas"<sup>22</sup> was seen, since calcification appeared in areas of fat before there was any microscopic evidence of degeneration. The calcium when first retained may have combined with fatty acids, but if so did not remain in this form, as the analysis of one of these deposits showed that all the calcium could be accounted for as calcium carbonate or tertiary calcium phosphate.

The disease process appeared from the histologic standpoint to have progressed until calcium had been deposited within fat cells and eventually replaced whole fat lobules. Once formed, these larger lime deposits became foreign bodies, stimulated fibrosis, caused formation of giant cells and slight lymphoid cell infiltration. Many nodules had coalesced into large masses, some had broken down and partially extruded their contents. Where this had occurred cicatrices had formed. We think that the presence of occasional hyalinized, thick-walled arteries was not an important etiologic factor. It is more probable that these vascular changes were secondary to the calcification and accompanying fibrosis. We agree with the conclusion of others<sup>19</sup> that inflammatory changes are not causative factors in these deposits.

Verse<sup>18</sup> studied and reported this disease process in a boy, aged 15 years, together with the postmortem findings. In addition to the subcutaneous calcareous nodules, he found that lime salts had been deposited in the interstitial connective tissue of muscle and in the connective tissue around muscle bellies, tendons and nerves. Calcification about the capsules of mesenteric lymph nodes was also observed. Otherwise there was no calcification of the internal viscera. From histologic study he thought that the calcium salts had been deposited in living connective tissue. As indicated by Roentgen ray examination, the present case also had marked calcification of the muscles of the arms and legs.

While we could find no microscopic evidence of previous tissue injury, it seemed important that this obscure process involved the regions of the body which are liable to trauma and are most subject to muscular activity. As previously noted, the more protected portions of the body, the thorax and abdomen were particularly spared.

Metabolic studies showed that this patient had an extraordinary ability to retain the absorbed calcium and phosphorus. This tendency was more marked in the case of calcium than phosphorus as demonstrated by the low fecal and urinary values for the former. Regardless of the calcium content of the diet or medication, the fecal calcium values remained extremely low, never exceeding 49 mg. per 3-day period. It seems fair to assume that a higher calcium intake would not have increased the fecal calcium values. Urinary calcium values as low as those observed during the control periods (1 to 7) are usually associated with a lowered serum calcium.<sup>23</sup> In the present case the low urinary calcium values were undoubtedly due to the marked affinity of the body tissues for calcium, thus resulting in a marked retention of this element. There was no evidence of increased calcium and phosphorus retention in the bones that could be demonstrated by roentgenograms. *The results obtained during Periods 24 to 25 suggest that when calcium is first*



FIG. 1.—Posterior view of patient showing numerous lesions in all stages of development over the buttocks and posterior aspects of the arms and legs.



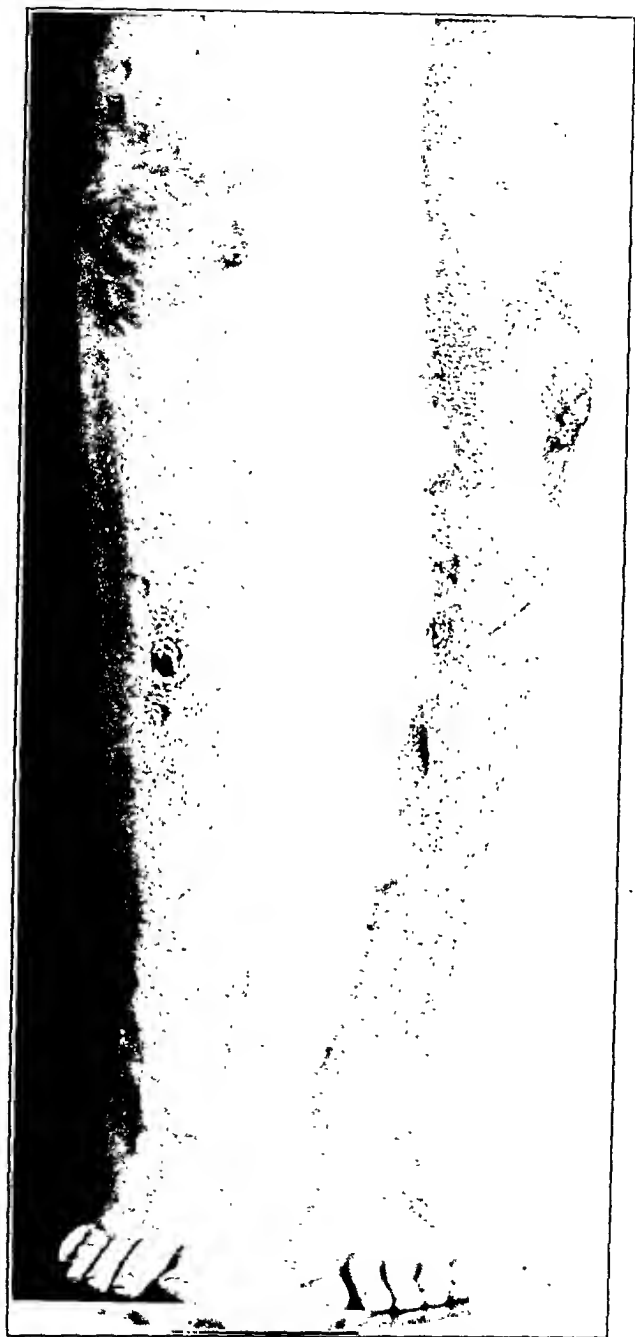


FIG. 2.—Anterior view of the legs. All types of lesions are seen. They are most numerous in the region of the knees.



FIG. 3.—Side view of the legs, showing flexion deformity of the right leg. The nodules on the outer aspect of the left knee have become infected.

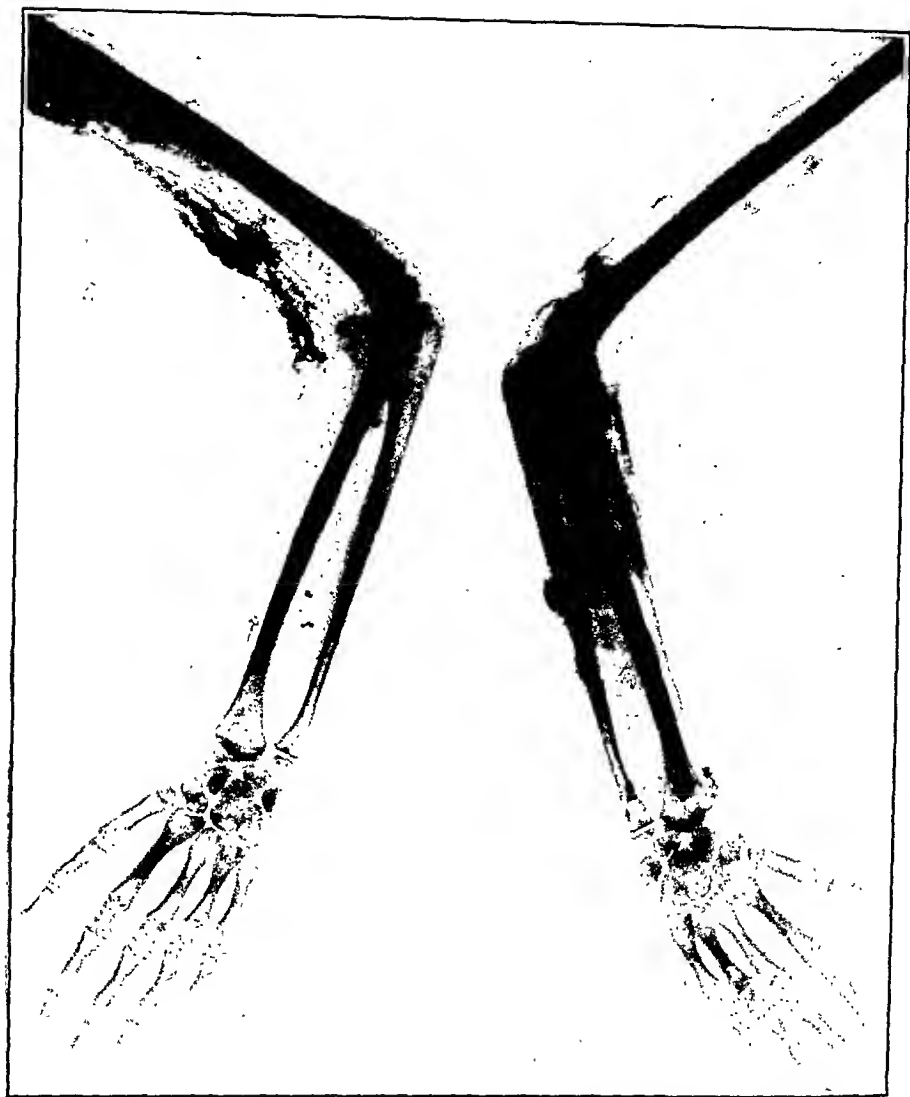


FIG. 4.—Roentgenograms of the arms showing the marked deposition of calcium in the subcutaneous tissue of the right forearm and the sheaths of the extensor muscles of the left forearm.

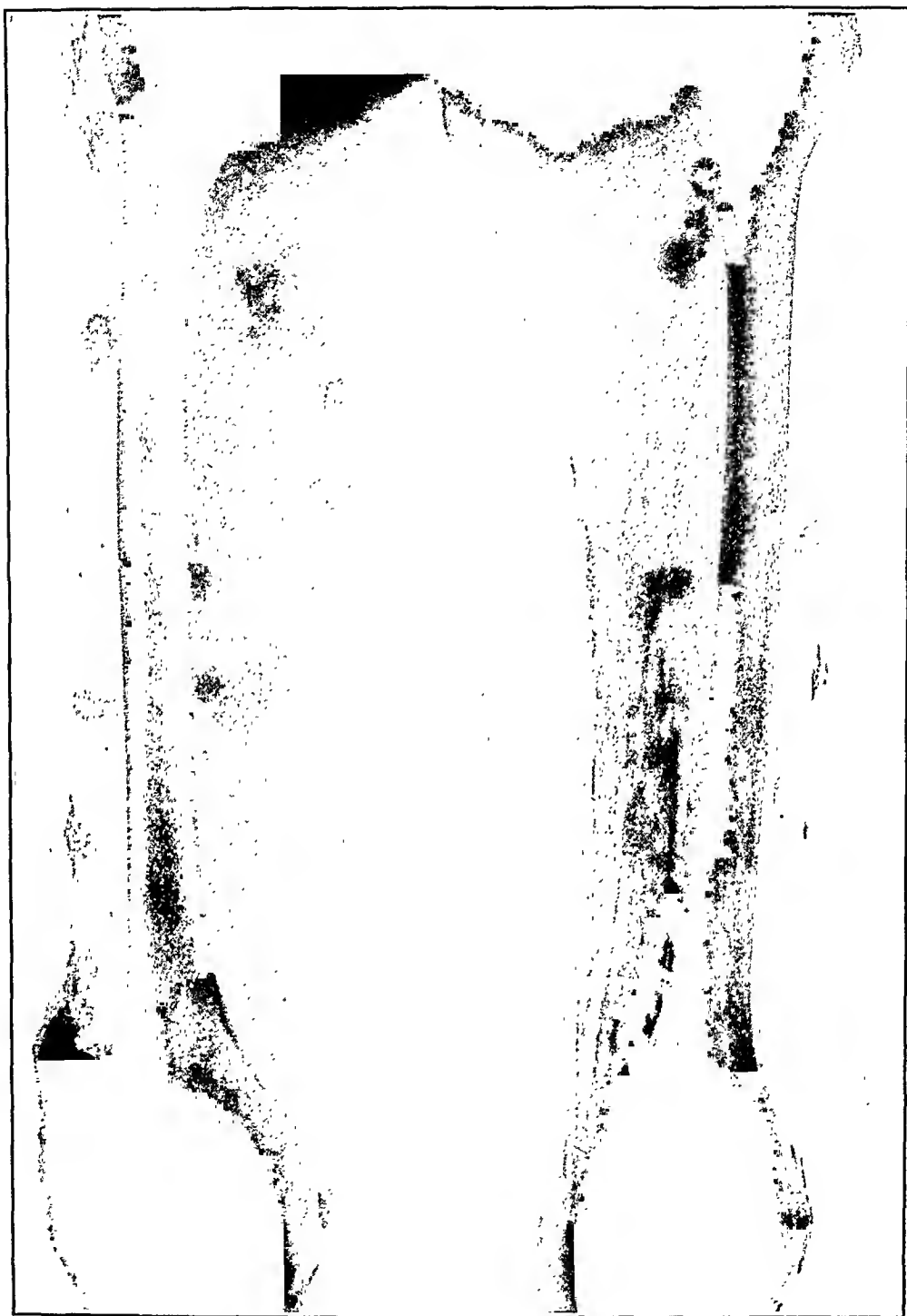


FIG. 5.—Roentgenograms of both thighs. The subcutaneous calcium deposits are well demonstrated. The ham-string muscles of the right leg show depositions of calcium in the sheaths surrounding them. This is seen to an even greater extent in the sartorius muscle.

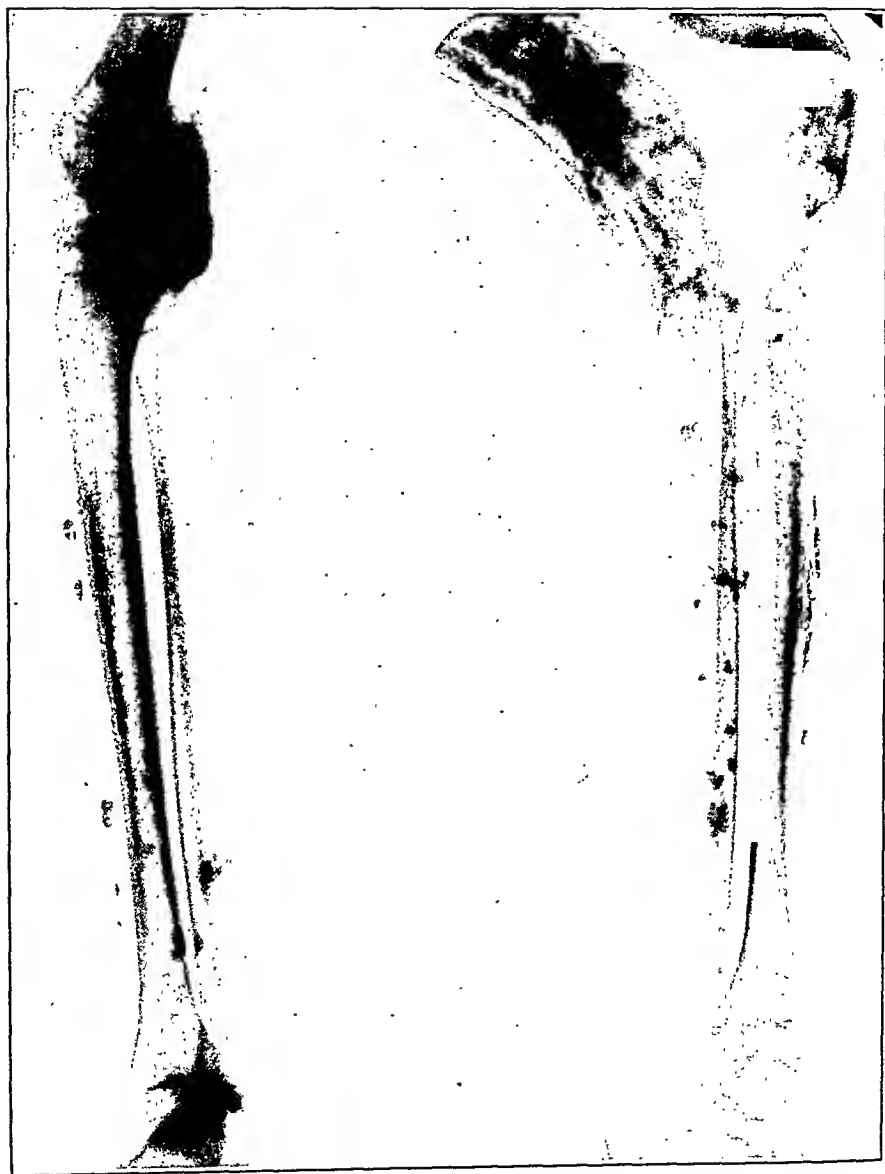


FIG. 6.—Roentgenograms of both legs. Calcium deposition in the subcutaneous tissues and muscle sheaths is easily seen.



FIG. 7.—Roentgenograms of both knees, illustrating the extensive calcium deposits in the region of both knees.

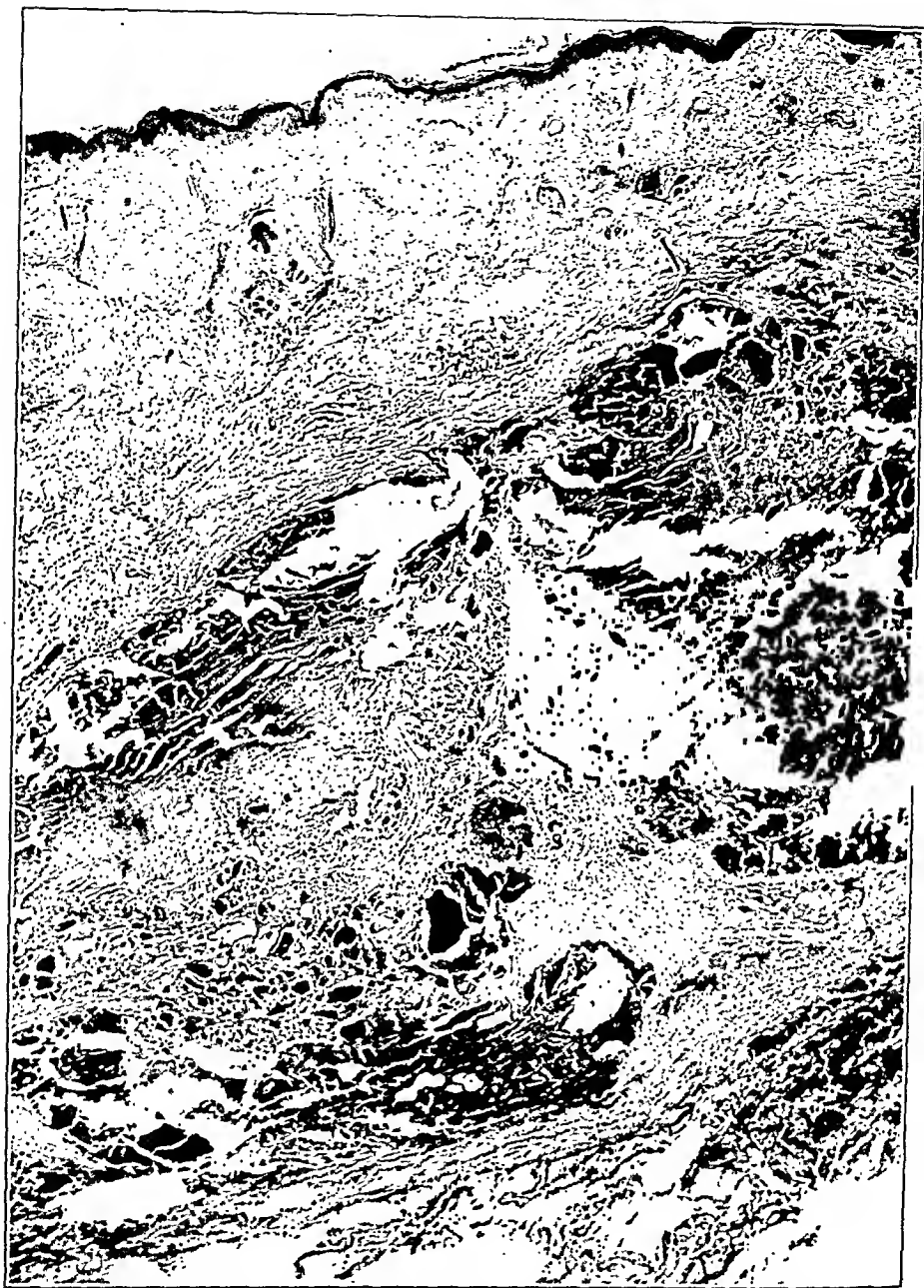


FIG. 8.—A photomicrograph with very low magnification showing a larger area of calcification in the subcutaneous tissue. Section was stained with hematoxylin and eosin.  $\times 28$ .

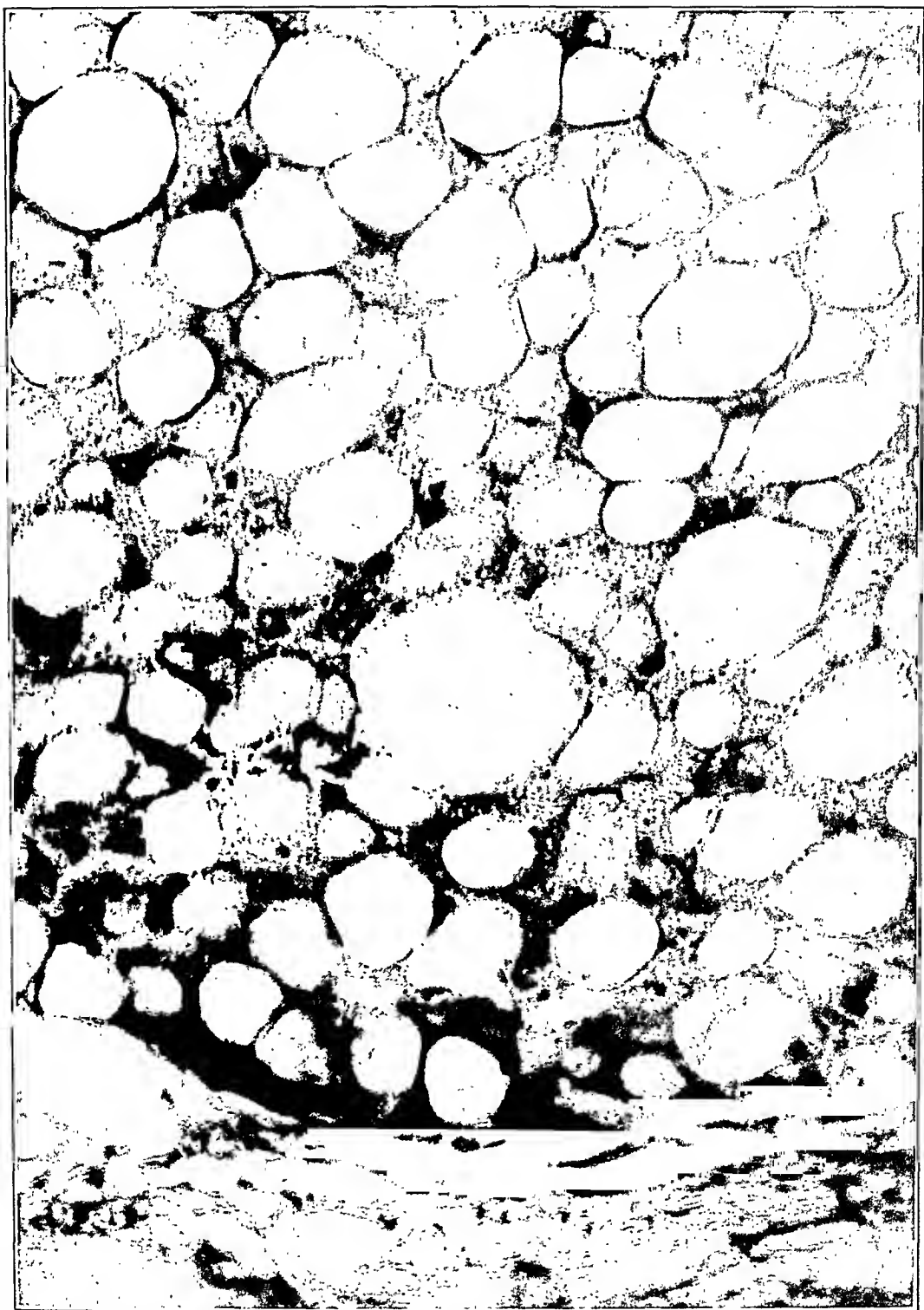


FIG. 9.—A photomicrograph ( $\times 300$ ) to illustrate what appeared to be the initial lesion, namely: a deposition of calcium particles about the periphery of intact fat cells.





FIG. 10.—An artery with thickened and hyalinized media in the proximity of a calcified area. Section stained with hematoxylin and eosin.  $\times 160$ .



FIG. 11.— Early connective-tissue proliferation and giant-cell formation in response to calcium deposit in fat.  $\times 160$ .

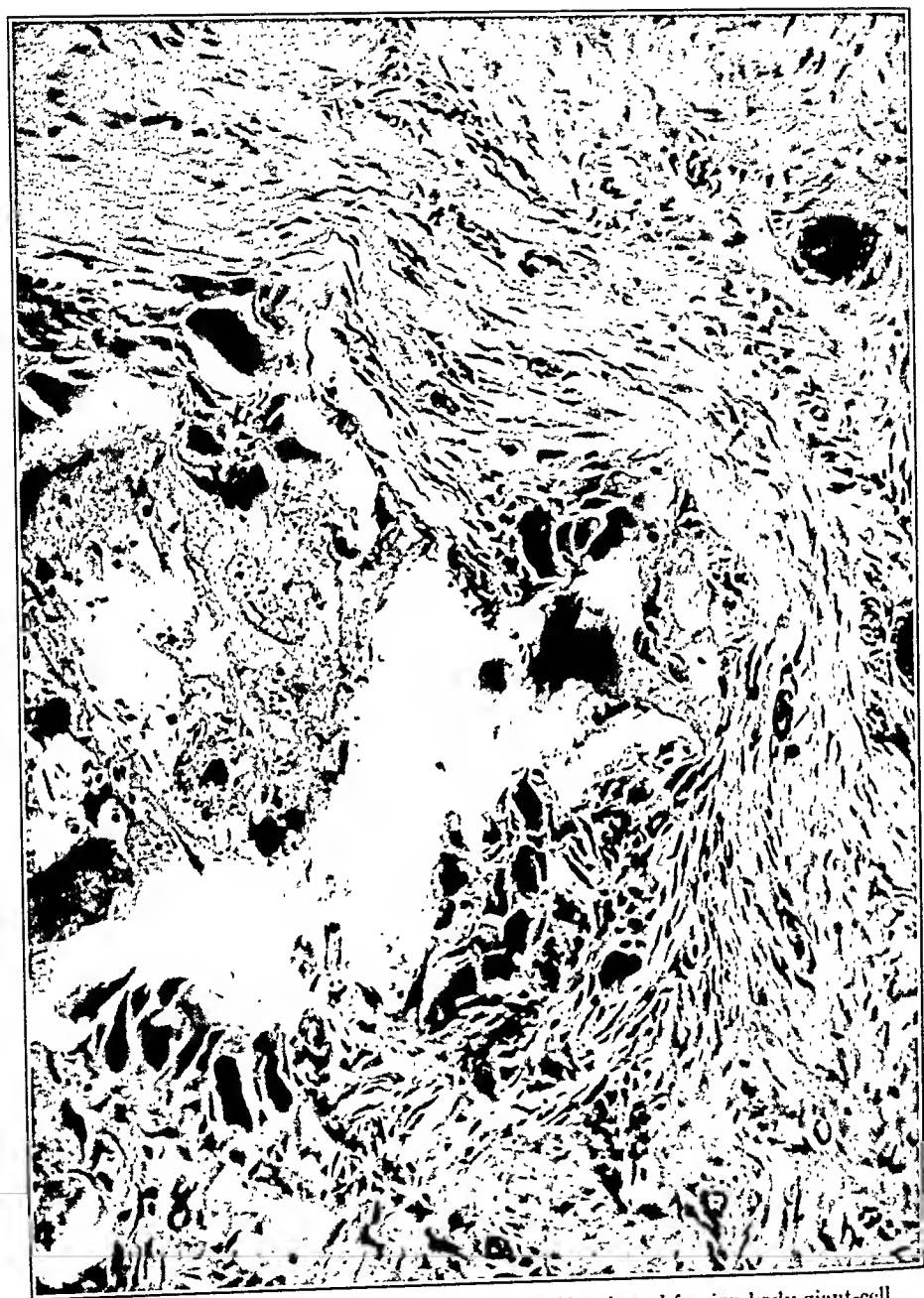


FIG. 12 —A photomicrograph ( $\times 210$ ) showing fibrosis and foreign-body giant-cell reaction about an area of calcification. Section stained with hematoxylin and eosin.

*deposited it does not necessarily have to be accompanied by phosphorus.*

We are unable to offer any explanation as to why this individual retained calcium and phosphorus to this degree. Irradiated ergosterol poisoning and parathormone overdosage are known to cause metastatic calcification, but this individual had no signs or symptoms which would justify such a diagnosis.<sup>24,25,26,27</sup> Furthermore, the calcification seen in the last-mentioned conditions occurs regularly in the kidneys, stomach, lungs, heart and bloodvessels; these organs were not involved in either our case or the one described by Verse.

As a result of the above considerations it seems fair to conclude that calcium and phosphorus metabolism is abnormal in these rare cases of calcification of the subcutaneous tissue. This is well shown by the excessive retention of calcium and phosphorus. The increased retention was evidently due to an unusual affinity of certain tissues for these elements. We are unable to state what intracellular changes, unrecognizable microscopically, preceded the deposition of calcium in these regions.

The belief that this condition is due in part to a general metabolic disturbance is contrary to the views of Tisdall and Erb<sup>19</sup> and of Wilens and Derby.<sup>1</sup> They reasoned that the normal blood values for calcium and phosphorus argued against a metabolic disorder.

However, this view seems scarcely tenable in the light of the calcium and phosphorus balance studies presented. The observed metabolic disturbance serves well to emphasize again that study of the serum calcium alone "merely shows the height of the 'calcium stream' but gives no indication as to its direction of flow."<sup>14</sup>

From our studies we would suggest the following treatment: the use of a diet inadequate in calcium in conjunction with a decalcifying agent, such as ammonium chlorid. However, the employment of such therapy over a long period of time might be expected to result in marked skeletal decalcification as well. The prognosis is at best, unfavorable.

**Summary.** 1. Further studies in a case of "calcinosis universalis" are reported.

2. Calcium and phosphorus balance studies indicated a marked tendency to retain the absorbed calcium and phosphorus in spite of normal blood calcium and phosphorus values. This tendency was more marked in the case of calcium than phosphorus.

3. Ammonium chlorid acidosis produced an increase in the urinary excretion of calcium and phosphorus.

4. Chemical analysis of a calcareous nodule removed at biopsy showed the presence of a negligible quantity of uric acid, a moderate amount of cholesterol and fatty acids, and calcium and phosphorus in the amount and ratio, one to the other, commonly found in adult bone and pathologic human calcification.

5. Histologic study showed no evidence of antecedent tissue necrosis, nor did it suggest any explanation for the abnormal calcium deposits.

6. The above results suggest that the basis of the disorder lies in an abnormality of calcium and phosphorus metabolism. It is suggested that the increased retention of calcium and phosphorus may be the result of local cellular conditions as yet undetermined.

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## TOXOID AS AN IMMUNIZING AGENT IN DIPHTHERIA.

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THE value of diphtheria toxoid in the active immunization of children against diphtheria is now well established. Reports on its use in over 1,000,000 cases demonstrate that it is an efficient and safe product to use.<sup>1</sup> Toxoid has enjoyed considerable popularity in France and in Canada, but its use in this country has been relatively limited. It is the purpose of this report to give the results obtained with toxoid in a controlled group of 358 children.

**Procedure. TOXOID USED.** The material employed in this study was a standardized commercial product.<sup>2</sup> It is prepared<sup>3</sup> by growing a virulent strain of diphtheria bacillus in broth which does not contain horse meat. This is to eliminate the possibility of sensitization to horse protein. At the end of a week this material is filtered and tested for its toxic value. Federal regulation requires that the toxin from which toxoid is made shall have an L+ (lethal) dose of not over 0.2 cc. or a minimal lethal dose of not more than 0.0025 cc. The "Lf" value, in other words, the amount of toxin in cubic centimeters which is required to flocculate 1 unit of antitoxin, or its reciprocal, the antigenic value, and the "Kf" value (flocculation time) are then determined. No toxin is used which requires more than 0.1 cc. to flocculate 1 unit of antitoxin. Such a toxin has 10 immunizing units, according to the French standard. After the toxin is selected a small amount of U. S. P. formalin is added to bring about complete detoxification in a reasonable period of time. This amount must not exceed 0.4 per cent. The formalized toxin is kept at a temperature of 39° C. At weekly intervals intradermal tests are made on guinea pigs to determine the rate of its detoxification. When it is believed that this has progressed sufficiently far the material is removed to the refrigerator and 5-cc.

portions are injected into a series of 300-gm. guinea pigs. When detoxification is completed no effect should be noted in the guinea pigs over a period of 30 days. The material is ready when 10 pigs injected with 5 cc. each show no signs of diphtheria poisoning at any time during a period of 30 days. The time required for complete detoxification will vary with each lot of toxin. The minimum antigenic requirements are that at least 10 guinea pigs, weighing 270 to 320 gm., shall receive subcutaneously the initial human dose. At the expiration of six weeks each of these pigs is injected subcutaneously with 5 minimal lethal doses of a stable diphtheria toxin. At least 80 per cent of these animals must survive for 10 days. The flocculation value of the finished product is then again determined, and if there has been any loss in flocculation value the product is discarded. The toxoid contains approximately 50 times the amount of media and bacterial protein that is present in the toxin-antitoxin mixture. The fact that toxoid is resistant to heat, retains its antigenic power, is nontoxic and free from horse serum makes it a most desirable preparation.

This study was carried out in the Children's Outpatient Department of the University of California Hospital, where they request that every well baby and child over 6 months of age be given a routine Schick test. To obviate errors in the technique of testing, the Schick testing is done one afternoon a week by a house officer who is on service for 6 months at a time. A fresh solution of Schick and control material is used each testing day. The Schick tests are read in 72 hours, and if positive the toxoid is then given in two doses of 1 cc. each, at an interval of 10 days. Re-Schick tests with controls are performed 3 months after the completion of the course of toxoid injections, and these re-Schick tests are read in most instances by the same man who administered and read the original Schick test. Every care is exercised in the performance of the Schick test and its readings, as these are the major sources of error.<sup>4</sup>

TABLE 1.—AGE OF PATIENTS TREATED.

Age.	Number.
3 mos. . . . .	3
5 " . . . . .	4
6 " . . . . .	12
7 to 12 " . . . . .	46
1 to 3 yrs. . . . .	94
3 to 5 " . . . . .	56
5 to 10 " . . . . .	74
10 to 15 " . . . . .	23
Total . . . . .	312

RESULTS. This study comprises data on 358 Schick-positive city children, between the ages of 3 months and 15 years. (Table 1.) Of these children 333 received two injections of 1 cc. each of toxoid at an interval of 10 days. Twenty-five children received only one

injection. Of the group receiving a total of 2 cc. of toxoid 327 (98 per cent) were Schick negative after a period of 3 months or more. Of the group receiving a total of 1 cc. 21 (84 per cent) were rendered Schick negative on retests. (Table 2.) These results correspond well with those found in other reports. (Table 3.) Our experience, as well as that of Weinfeld and Cooperstock,<sup>5</sup> would indicate that two injections of 1 cc. each of toxoid are as effective as 2 cc. given in three doses. It has the added advantage

TABLE 2.—RESULTS WITH TOXOID.

	Total No.	Negative after toxoid.	
		No.	Per cent.
Positive Schick tests . . . . .	358	348	97
2 cc. toxoid . . . . .	333	327	98
1 cc. toxoid . . . . .	25	21	84

TABLE 3.—COMPARATIVE STUDIES IN IMMUNIZATION WITH TOXOID.

Author.	No. of cases.	Dose, cc.	No. of injections.	Interval.	Per cent immunized.
Harvier and Requin <sup>8</sup> . . . . .	88	0.5	2	3 weeks	95
		1.0			
Ramon and Helic <sup>1</sup> . . . . .	..	0.5	2	3 "	90 to 95
		1.0			
		0.5			
		1.0	3	3 "	97 to 100
		1.5			
Moloney and Frazer <sup>6</sup> . . . . .	66	0.5	2	1 month	70
		0.5			
Zingher <sup>14</sup> . . . . .	100	0.5			
		0.5	3	2 weeks	98
		1.0			
		0.5	2	...	86
		0.5			
		0.5	1	...	60
Roubinovitch, Loiseau and Lafaille <sup>12</sup> . . . . .	130	0.5	1	...	37
	53	0.5	2	3 "	81
		1.0			
	79	0.5	3	3 "	88
		1.0			
		1.5			
Bloomberg and Fleming <sup>9</sup> . . . . .	208	0.5	2	1 month	68
		0.5			
	38	0.5	2	1 "	84
		1.0			
	32	0.5	3	1 "	94
		1.0			
		1.0			
Schwartz and Janney <sup>11</sup> . . . . .	128	0.5	3	3 weeks	98
		1.0			
		1.0			
Weinfeld and Cooperstock <sup>5</sup> . . . . .	89	1.0	2	3 "	92
		1.0			
	15	1.0	1	...	46
Dick and Diek <sup>13</sup> . . . . .	100	0.5	3	2 "	94
		1.0			
		1.5			
Author . . . . .	333	1.0	2	10 days	98
		1.0			
	25	1.0	1	...	84



of saving time and also the pain of one injection. Results given in Table 3 suggest that when a total of 2 cc. of toxoid has been given one may expect from 90 to 98 per cent negative Schicks on retesting. When 1 cc. only is given the percentage will be below 90 per cent. Toxoid has not been in use for a sufficient period of time to determine the length of the immunity produced. Three cases of this series were retested after an interval of 3 years and found to be Schick negative. (Table 4.)

TABLE 4.—RESULTS OF SCHICK RE-TESTS AFTER TOXOID.

Total number of children Schick retested	No. Schick retested.	No. Schick negative.	Per cent negative.
At 3 months . . . . .	358	348	97
At 4 " . . . . .	205	195	95
At 5 " . . . . .	90	90	100
At 6 " . . . . .	28	28	100
At 6 " . . . . .	17	17	100
At 6 " to 1 year . . . . .	15	15	100
At 3 years . . . . .	3	3	100

REACTIONS. Both local and general reactions are seen with toxoid as with the toxin-antitoxin mixture. The reactions may occur after the first, second or third injection of toxoid. Weinfeld and Cooperstock<sup>5</sup> state that local reactions are rare and general reactions are never seen in children under 7 years of age. Maloney<sup>6</sup> and Frazer believe that reactions are very rare in children under 8 years, while local reactions occur in about 25 per cent of children over 8 years of age. Ramon<sup>1</sup> finds that reactions are rare under 8 to 10 years, and suggests that they occur principally in those children with a pseudo-Schick reaction. He says from 20 to 40 per cent of persons over 10 years have slight reactions; from 10 to 15 per cent have fair reactions and from 1 to 5 per cent strong reactions. Fitz-Gerald<sup>7</sup> summarized an experience with 10,600 preschool children and says that 2 to 3 per cent had fairly marked reactions and 25 per cent had slight local reactions. Harvier and Requin,<sup>8</sup> in a group of 235 children, observed feeble reaction in 21 and general reactions in 35.

In a study of 278 children Bloomberg and Fleming<sup>9</sup> saw no reactions in children under 6 years of age either from the 0.5-cc. or the 1-cc. dose. Ramon<sup>1</sup> has collected data on over 1,000,000 injections of toxoid and has not found a serious accident or fatality.

The reactions produced by toxoid are probably due to the fact that it contains a relatively large amount of media and bacterial protein. It is thought by some workers<sup>1,5</sup> that persons who react to toxoid have been sensitized in some way to these specific proteins or that the reactions may be considered as nonspecific protein reactions. This would account for the reactions occurring so rarely in younger children and so readily in those persons showing a pseudo-Schick reaction. Moloney<sup>10</sup> has shown that those persons who react to toxoid are more readily immunized than nonreactors.

Two cases in this series who had general reactions were immunized by 1 cc. of toxoid given in one dose.

In Table 5 we have listed the children who gave general reaction together with a note as to a history of allergy in these cases. J. F. is an exceptionally young child to react to toxoid, being only 5 years of age. T. D. was given toxoid and in 3 hours developed such a severe asthmatic attack as to necessitate hospitalization.

TABLE 5.—GENERAL REACTIONS FROM TOXOID.

Case.	Age, yrs.	Sex.	Reaction.	Allergy.	No. of injections.	Repeated Schick.
J. F. . . .	5	M	General	No	1	Negative.
W. C. . . .	7	M	General	No	2	Negative.
T. D. . . .	10	F	General	Asthma	1	Negative.

Three patients in this series had general reactions. These came on within 8 hours and lasted for about 24 hours. About the site of injection a large area of redness developed, which was tender and painful to touch, and caused some discomfort in movement of the arm. General symptoms were anorexia, malaise, nausea, headache and marked irritability, with some slight rise in temperature. In 1 of these cases a typical asthmatic attack was precipitated by an injection of toxoid. It has been suggested by Weinfeld and Cooperstock<sup>5</sup> that persons with an allergic background may react to toxoid more readily than those without such a history. In a group of college students they found that of those persons with an allergic history 40 per cent gave reactions to toxoid as against 16 per cent in those without an allergic back ground.

Schwartz and Janney<sup>11</sup> feel that allergy does not play such a prominent rôle in preschool children, as in their study of 128 children there was only 1 reaction. Their series included 14 cases of eczema, 15 of seborrheic dermatitis and 1 each of asthmatic bronchitis and hay fever. They are, therefore, of the opinion that an allergic makeup does not necessarily provoke a toxoid reaction in a preschool child.

A review of all the cases of allergy in our clinic was made, and 7 patients were found who had received toxoid. Of this number only 1 had a reaction. While this is too small a group from which to draw conclusions, it suggests that in children, age and the chance for acquired sensitivity are of equal or more importance than allergy in the production of reactions. Children under 8 years react much less frequently than those over this age.

The difference in the number of reactions reported by various workers may possibly be explained by the difference in the toxoid used. The earlier preparations gave more reactions. The present methods of preparation and refinement with the resulting minimal amounts of culture and media protein give fewer reactions. Local reactions in this series were so slight that in no case did we have anyone who objected to the second dose of toxoid being given.

**Summary.** The use of toxoid in the active immunization of 358 children against diphtheria is reported; 333 children received 2 cc. of toxoid and 98 per cent were rendered Schick negative; 25 received only 1 cc. of toxoid and 84 per cent were immunized. In this series toxoid was given in two injections of 1 cc. each at an interval of 10 days. This routine was found to give satisfactory results.

Both local and general reactions are seen with toxoid. Age, the possibilities of sensitization to the protein of the Klebs-Loeffler bacillus or the media proteins and a background of allergy are all factors concerned with the production of reactions. Children under 8 years react much less frequently than children over 8 years of age.

From our own observation and on evidence in the literature, one may expect from 90 to 98 per cent negative Schick reactions after a total of 2 cc. of toxoid has been given. When a total of 1 cc. only is given the number of Schick negative results will usually be below 90 per cent.

**Conclusion.** Toxoid is a safe, reliable and efficient preparation to use in the immunization of children against diphtheria.

The author wishes to acknowledge the generous supply of toxoid which was furnished through the courtesy of Dr. J. G. Fitz-Gerald, Connaught Laboratories, University of Toronto, Toronto, Canada, at the initiation of these studies. Thanks are also due Dr. Robert Cutter, Cutter Laboratory, Berkeley, Calif., for his interest in the development of toxoid and for his many suggestions during the course of this study.

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# TOXICITY AND RATE OF ELIMINATION OF ORGANIC ARSENICALS (STOVAR SOL AND TREPAR SOL) IN THE TREATMENT OF ENDAMEBIASIS.\*

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THE convenient method of treating endamebiasis by the oral administration of organic arsenicals has led to more or less indiscriminate use of these drugs. In view of the vast amount of experience that has been derived from the use of arsphenamin, it is difficult to understand the free and easy manner in which stovarsol and treparsol have been used. A review of the reported complications in the use of these drugs convinces us of two facts: (1) That the drugs are continued in spite of warnings of intolerance, and (2) that certain persons are very sensitive to arsenic in any form.

There are numerous reports of toxic erythema and even exfoliative dermatitis from the use of the two drugs. In most cases the cutaneous reaction is manifest after only small or moderate amounts of arsenic have been taken. Dargein and Doré reported a death from treparsol. Their patient was an elderly man, with active syphilis of the central nervous system. Treatment was begun with the arsenical and although the dosage was moderate, yet an acute break occurred and the patient died in coma. This resembles the danger of the use of arsphenamin in syphilis of the central nervous system. They considered the death as due to a Herxheimer reaction. Milan and Garnier reported a death from treparsol as the result of administering treparsol to a young woman with syphilis. She was given 4 tablets (1 gm.) daily for 9 days, when delirium developed and she died in 24 hours. The dose in this case was greater and the treatment more prolonged than we have used for endamebiasis. May reported the first death from treparsol. In this case the patient began to show signs of intolerance to arsenic, but she continued using the drug, and in 2 days became unconscious and died in coma. La Terza, in 1930, reported experiences from Brazil, with treparsol, namely, 2 cases with 2 deaths.

In the literature we were able to find records of only 2 deaths attributed to stovarsol poisoning (Willner and Meleny). Porot

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reported on sensory disorders and pseudotabes due to stovarsol. In 2 cases stovarsol had been used intermittently over a period of months in an endeavor to eradicate *Giardia lamblia*. The symptoms of involvement of the central nervous system came on insidiously, beginning with rheumatic pains, and continuing until there was marked disability. The third patient had taken 0.25 gm. stovarsol daily for 10 days because of amebic colitis. Shortly after the conclusion of this one course, peripheral neuritis was manifested. Further reference to this complication was not found. We have observed 1 severe and 1 mild case of peripheral neuritis following the ingestion of stovarsol but none from treparsol.

In the first case acute amebic colitis had been controlled by 3.5 gm. of stovarsol. The patient was dismissed from observation, and two additional courses were prescribed, with 10-day intervals between courses. A few weeks after the last course bowel symptoms recurred and a fourth course was taken without our knowledge. The patient did not respond well; the dysentery was not as completely controlled, and aching appeared in the legs. He decided to take a fifth course. Following this severe symptoms of peripheral neuritis developed, which totally incapacitated him. The neuritis persisted for months. The urine was examined for arsenic 3 months after the last stovarsol was taken. Arsenic in appreciable quantities was found. The colitis itself apparently was cured by yatren; this was confirmed several months later.

In the second case the patient had amebic colitis. He received 7.5 gm. of stovarsol in two courses. Fifty days after the last course arsenic was found in the urine. The mild neuritis which had developed subsided in a short time. Toxic erythema developed after the first course, but cutaneous reaction did not occur after the second course.

In both these cases warning signs were put out. The first patient might not have escaped neuritis, but failure to control the colitis with three courses of stovarsol should suggest a change of treatment. In the second case the cutaneous reaction warned of questionable tolerance to arsenic.

To emphasize the individual factor in such a reaction, it may be noted that we examined the urine of another patient 13 days after the completion of a course, consisting of 3.75 gm. of stovarsol. Arsenic was not present in the specimen.

In our experience with these two arsenicals there have been no deaths. Two cases of peripheral neuritis have been noted. We also have data concerning six cutaneous reactions in 123 cases in which treparsol was used and of four cutaneous reactions in 130 cases in which stovarsol had been used during the last 4½ years. In 9 of the 10 cases toxic erythema occurred, which subsided in 3 to 5 days. In the tenth case there was enough cutaneous reaction to prompt the diagnosis of exfoliative dermatitis. This patient

recovered in a week and did not suffer further ill effects. The percentage of cutaneous reactions with treparsol (4.8 per cent) is somewhat higher than with stovarsol (3 per cent). We have prescribed these arsenicals for many other patients, but data are available only concerning the 253, all of whom received from 3.5 to 16 gm. of the drugs.

The 2 cases of peripheral neuritis developing subsequent to the use of stovarsol prompted us to consider the rate and channel of elimination of the arsenic of this drug. Accordingly, the urine and feces were collected for a period of 7 days from 5 patients who had received 3.5 gm. or more of stovarsol. Attempts to determine quantitatively the arsenic excretion by the ordinary Gutzeit procedure were unsuccessful, however. Except for the fact that qualitatively it was found that arsenic was still being excreted in the urine at the end of 7 days, the experiment did not furnish the information which we desired, namely, the ratio of urinary excretion to fecal excretion.

Following the development by one of us (Osterberg) of the electrolytic Gutzeit procedure for the estimation of arsenic, it was decided to conduct similar elimination studies following the administration of treparsol, since our interest has been focussed on this drug.

Four patients of the group receiving treparsol were selected for observation. A single course of treatment consisted of the daily ingestion of 0.75 gm. of treparsol for 4 days. It was felt that the degree of absorption of the drug from the intestinal tract was dependent on the physical dispersion; hence, it would seem the more desirable to use the compound in the form of a finely ground powder rather than as a tablet, as it is commonly dispersed.

However, in order more closely to simulate the actual conditions of treatment with this drug as it is commonly practised, it was decided to request 2 of the patients to swallow the entire tablet without chewing and the remaining 2 patients to chew the drug thoroughly before swallowing.

From the results of the determinations by the electrolytic Gutzeit method, it was found that the major portion of the arsenic is eliminated in the feces. When the treparsol tablets were swallowed without chewing the ratio of arsenic in the urine to that in the feces was 1 to 9 and 1 to 16. In the cases in which the tablets are thoroughly chewed the ratio of arsenic in the urine to that in the feces was 1 to 3.

In all cases 90 per cent or more of the total arsenic was recovered by the third day following the last ingestion. The absolute amount and the relatively greater proportion of arsenic in the urine in the cases in which chewing of the drug was resorted to indicate that the physical condition of the drug is of prime importance in its absorption. The amount of arsenic remaining in the feces repre-

sents unabsorbed treparsol rather than arsenic excreted by this route.

Realizing that individual variations to arsenic exist, we hesitate to postulate that treparsol, used in doses of 0.25 gm., two to three times a day, with a total amount of the drug not to exceed 3 gm., is preferable to stovarsol solely because, as we have shown in the study of elimination of arsenic under treparsol treatment, the arsenic was eliminated in a period of 7 days and also that peripheral neuritis did not result, whereas if patients were under stovarsol treatment arsenic was present weeks and even months after discontinuing treatment, and peripheral neuritis was encountered as a complication. However, we consider that since the cutaneous reactions occur in about an equal percentage, and as we have not known of peripheral neuritis to occur after the use of treparsol, the clinical experience seems to bear out the study of elimination in favor of treparsol.

Chen, Anderson and Leake have recently reported on the rate of urinary excretion of stovarsol and carbarsone. In 1 case 2.75 gm. of stovarsol was administered in 6 days, and in the second case 3.5 gm. was administered in 7 days. In the former, 29 per cent of the arsenic administered was recovered from the urine in 14 days after treatment was begun; in the latter, 17 per cent was recovered in 10 days. These observations indicate the persistence of arsenic in the urine; however, the amount remaining is uncertain as data relative to the arsenic excreted through the bowel was not obtained.

#### SUMMARY OF RESULTS.

Arsenic eliminated, mg.			Ratio	Arsenic in urine Arsenic in feces
Urine.	Feces.	Total.		
192	595	787	1 to 3 treparsol chewed.	
184	546	730	1 to 3 treparsol chewed.	
45	741	786	1 to 16 treparsol not chewed.	
70	645	715	1 to 9 treparsol not chewed.	

**Conclusion.** New remedies are constantly being sought in the treatment of endamebiasis. It is possible that nonarsenical remedies, such as anayodin (yatren), or more recently dihydranol, will supplant the arsenical drugs. Emetin will continue to prove a bulwark for controlling the acute phase of the disease, but we feel that it must be used in conjunction with other preparations to effect cure in a large percentage of cases. We have found emetin and treparsol very satisfactory; they constitute the first line of defense unless there are contraindications to their use. Arsenic has proved to be such an effective parasiticide that it will probably continue to be used, although a less toxic arsenical preparation may be developed.

The rate and route of elimination of arsenic following the administration of treparsol has been determined in 4 cases selected from a group of 253, in which the patients were suffering from endamebiasis.

The fineness of the ingested drug determines to a large degree the extent of its absorption and the ratio of arsenic in the urine to that in the feces.

Our data tend to show that treparsol is more rapidly eliminated than stovarsol and that the possibility of untoward sequelæ developing is lessened with the former drug.

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### GUIDES TO THE PREVENTION AND TREATMENT OF THE SIMPLER NEUROSES.

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In this day of overspecialization the internist holds a rather unique position in medicine. He alone is privileged to consider his patient as a whole; to investigate without prejudice not only the body but the mind; and if an explanation for symptoms be not found after appropriate physical examinations, to seek their cause in the patient's relation to his environment. If he does not exercise this prerogative, a valuable opportunity has been not only neglected, but more often irreparably lost. The patient who leaves his doctor's office with psychogenic symptoms unrecognized travels thereafter like a derelict from one specialist to another, and often finally reaches the charlatan, who at least takes the symptoms at face value and offers hope of cure.

Why does the internist so often fail to accept his responsibility and make no adequate study of his patient's emotional life? I believe there are two reasons. In the first place most internists



believe that all cases of neurosis demand a great many hours of treatment, and that neither he nor the patient can afford the time; secondly, he often does not know what to say, how to get at the facts or what to do about them if discovered.

With full recognition that prolonged treatment is essential in many cases, it is my belief that a very large proportion of these patients both can and must be helped by the internist if they are to be helped at all. Complete cure, which would imply entire self-understanding, certainly is often not attained. But relief from symptoms will result in numerous patients, after a very few hours' work. Even if entire relief be not secured, the subject of psychotherapy is opened up. The patient at least partially understands his problem and may accept a suggestion that he continue further with a psychiatrist the work already begun.

The physician's greatest stumbling block is lack of thorough psychiatric training. This defect in medical education is not insuperable. The internist cannot undertake a complete psychoanalysis, but he should be able to understand the various types of difficulties frequently underlying neurotic symptoms, and should have a practical knowledge of the simpler methods of therapy.

At the outset both the patient and physician must be convinced that organic disease does not exist, or if it be present, that it cannot wholly explain the symptoms. The patient, moreover, must be made to feel that his physician believes his symptoms to be real, as they are; not imaginary as they so frequently are labelled even today. Lastly, the physician must be able to explain how real symptoms can occur in the absence of organic disease, and must uncover, if he can, the sufficient cause for symptoms in his patient's unconscious emotional life.

It is usually wise with such cases to begin by describing the physiologic changes popularly known to be associated with emotional tension; the dilatation of skin arterioles and capillaries caused by shame and the constriction caused by fear. Many patients have experienced frequency of urination or diarrhea in relation to nervous tension, or loss of appetite and nausea preceding an after-dinner speech or dramatic performance. It is emphasized that the diarrhea or nausea are as real under these circumstances as diarrhea or nausea accompanying dietary indiscretion or disease of colon or stomach. It may be valuable to illustrate the changes in function accompanying emotional disturbance by quoting Cannon's experiment with the cat, in which under Roentgen ray the normal gastric peristalsis was seen to cease when a dog was brought into the room.

The patient is thus convinced not only that he and his symptoms are being taken seriously, but that varied symptoms may be caused by emotional strain, notably by fear. At this point he may seize the opportunity to volunteer an explanation of his own symp-

toms; and although this attempt is usually abortive, at times a superficial neurosis may thus be entirely resolved, the patient saying that he "knows what is the matter with him," and then pouring out a story of worry or fear. Sometimes the unrecognized fear of a specific disease (often cancer) will be brought to light, the patient for the first time daring to meet this fear in the open and ask his physician for the truth.

If the problem is not solved at this point, and it usually is not, I find it wise to take time to review for the patient various types of emotional difficulty which occur in human beings, and to explain how symptoms may result from them.

In the World war we were all familiar with physiologic disturbances in otherwise normal organs. For instance, certain soldiers complained of precordial pain, dyspnea and rapid heart action, all symptoms of heart failure, yet when the heart was examined it was found to be without disease. It is interesting that the symptoms for the most part developed not at the front, and not in deserters, or men retired because of injury, but in those men behind the lines who had to look forward to a return into danger. Such a man was faced with two alternatives: either he must expose himself to injury or lose his self-esteem. Faced with this dilemma, a coward might flee, achieve safety and suffer no neurosis; or a particularly brave man return to duty in spite of fear; but for many neither alternative was possible. The inevitable unconscious conflict resulted in bodily symptoms, whereupon a third alternative became apparent: to escape peril without loss of self-esteem through symptoms. The various symptoms resulting from the soldier's conflict became the means of saving his most precious possessions, life and self-esteem. What wonder the symptoms were unconsciously embraced and retained!

Many neuroses in civil life follow a similar causative pattern. Life appears overdangerous. Go forward we must, but to go forward and retain self-esteem appears to the subconscious mind too difficult. The consequent impasse results in physical symptoms, and the symptoms are again unconsciously welcomed as a solution of the problem. Is it not our duty as physicians to discover why such patients have grown to fear life, and to prove to them that the danger sensed exists not of necessity, but because of a mistaken point of view, usually the result of bad training in infancy and childhood?

The child's early training even today is often unfortunate. Children are either made too much of, or neglected and discouraged at the outset. In either case they very early develop a disproportionate desire for power. The child who is made the center of attention soon begins to enjoy this central position above all else, and will make every effort to hold it. Misbehavior in early childhood often enables him to focus upon himself the attention of

which he feels in need. He may refuse to eat, or defecate. He may have tantrums. Whatever causes evident consternation to his parents is grist to his little mill. When such a child first enters school he is unhappy. He misses his home where he was a central figure and, symptoms coming to the rescue, he often succeeds in regaining this friendly country. People speak of him as being "too sensitive" for school. Such a child will be shy, will take responsibilities overhard. Because he has never learned to accept inferiority, to fail courageously, he finds himself in unconscious and sometimes conscious terror of failure. To be at peace with himself he must excel. Already we see such a child—too ambitious for success—living before an audience which he must always please. The audience consists of himself and all the world besides, and before this audience he dare not fail.

Parents, moreover, often make the mistake of loading down their children with their own ambitions. Frustrated themselves, they come to feel an exaggerated satisfaction in their children's "successes." The child, in turn, sensing that much is expected of him, and afraid to disappoint both himself and his parents, whips himself still further toward his already crystallized though usually unconscious goal of superiority.

It is easy to understand that for such children life is a dangerous place. The attempt to achieve a goal of individual superiority necessitates a constant battle with other individuals, most of whom have an identical goal for themselves. Life becomes thus a continuous competition, with peace of heart dependent upon success. No wonder such a child labors under tension, too often ill-understood. This tension is further intensified if the child has grown to demand not only a sense of superiority as his goal in life, but absolute superiority, *i. e.*, perfection.

A child so trained faces a future where, to achieve peace of heart, he must maintain this sense of perfection, and a sense of perfection is a very fragile thing. His constant fear is lest he see himself or be seen by others inadequate, imperfect. As he grows older and avoidance of mistakes becomes increasingly difficult, the child begins to restrict his world to those who look upon him with special consideration. He plays with himself rather than with others, prefers to stay with mother or father of whose good opinion he is certain, rather than risk the often unfavorable opinion of boys or girls of his own age. Such youngsters often grow up without the training for marriage which should result from the normal attractions toward the opposite sex of childhood and early youth. Self-conscious and shy, with feelings of inadequacy becoming constantly more insistent, the boy or girl approaches unprepared the peril of matrimony.

For marriage is in fact a supreme danger for an individual so trained. Upon what stage is a perfect part more difficult to play

than upon the stage of matrimony? If a sense of perfection be essential, does not wisdom urge escape from marriage at any cost? The escape is sometimes partly conscious, sometimes wholly unconscious. Many reasons are discovered to make marriage inadvisable. A woman may idealize men to such a degree that no man will ever come up to her expectations; or a man may fall in love only with married women or with a woman already engaged. Toward girls with whom there are no obstacles against marriage, he feels no attraction. Again certain men or women retreat to safety by feeling no interest whatever in the opposite sex. Thus by devious means, the threat to self-esteem is circumvented. Such a man or woman may be totally unconscious of the mechanism at work, but marriage is effectively discarded.

Difficulties in the narrower sexual sphere often have a similar etiology. Sex feeling is inhibited by fear. Most men and women who believe themselves sexually inadequate (or prove to be so in marriage) are inadequate because of fear. The dread of discovering themselves and being discovered other than perfect as a lover interferes with the physiology of propagation and may completely inhibit it. When the universal sex drive is felt and the outlet for its expression blocked, the period of self-gratification or of homosexuality may be prolonged beyond the normal, and such an individual come to look upon himself as a pervert, this fear, in turn, often interfering with all normal sex adjustment.

An important factor retarding or preventing normal adjustments to life is the conflict resulting from parents' shame or fear in discussing the question of sex with their children. It is almost incredible that men and women, all of whom have been conceived and born in an identical manner are unable to tell their own children about conception and birth, but such is the case even today. The generations who associated sex feeling with shame and evil seem to have handed on their fears, like a disease, to the parents of the present. And although the modern parent is more conscious of his duty to educate his child along these lines, such education is undertaken too often with trepidation and hesitancy or with such deliberate boldness that the child receives an emotional shock as a result. It is not what parents tell their children in so many words, but the state of mind which accompanies what is told that is important. A child may not understand, or may forget the facts, but he never forgets the emotional tone of the telling. If parents are not themselves adjusted to the subject of sex, wise though their words may be, their own shame and fear will be inevitably sensed by the child as the primary association with sex. For years thereafter, and perhaps forever, any sex feeling may be regarded as something shameful. If the ideals be high and self-esteem held dearly, such children are doomed to conflict between their normal sex drive and the necessity to retain their self-esteem. Neurotic symptoms are

frequently the result, and again the adjustment to marriage is often seriously endangered. Many women and some men are frigid in the marriage relation because sex feeling from early childhood has been associated in their minds with shame and evil.

In presenting some such outline of the mechanisms of neurosis to each patient, the analyst might say the cart had been placed before the horse, but for practical purposes a scaffolding of hypothesis must first be raised and the details later applied.

To make the patient aware of the fear or the unconscious conflict responsible for his own difficulty is the important step. By asking him to recall his earliest memories, by investigating his relationship to the other members of his family, by inquiry into early sex education and experiences, this can usually now be accomplished. The patient may often be brought to realize that his situation is in fact a very natural one, perhaps the inevitable result of early experiences and the repressions which have followed in their wake. If it is found that the patient's unconscious goal has been to preserve at any cost a sense of superiority necessitated by a false goal in life, and if such a patient can be made to realize that peace of heart should depend upon his doing the best he can and not upon personal perfection, the neurosis, no longer necessary for the protection of self-esteem vanishes.

**Summary.** The ideal of medicine has ever been and (in spite of necessary and laudable specialization in various fields) remains today the treatment of the individual patient as a whole. It is as human beings that we must function in this world—as human beings, that we must work and love and play—not as brain dissociated from heart, nor yet as heart dissociated from body. It is overconcentration upon the importance of a single organ considered apart from its relation to the entire body—in overemphasis of a symptom as against the cause—or, indeed, even of the cause as against the symptom—that the weakness of modern medicine lies.

The last 25 years have seen the rise of the "science" of psychiatry. We observe the various schools at war with one another—the camp of Freud repudiating the tenets of Adler, the followers of Adler repudiating the tenets of Jung. At best the various schools are unable to agree upon that human impulse which is the fundamental cause of all neuroses. Is it not possible that no one "cause" is always so—but that each alienist is sometimes right—and sometimes wrong?

It seems to us that it is the place of the internist, of the physician who is specialist in no one field but doctor in many, at least to attempt to discern, combine and apply what is good in the conclusions of each school. True it is that life is too short and the time of both physicians and patients too fleeting for wise selection and application to be always adequately and unerringly made—but it is the privilege as well as the duty of every internist to see his patient

as a human being—to recognize the fact that a sick body is often the result of a sick mind, as a sick mind is frequently the companion of a sick body.

Can we blame the psychiatrists for quarrelling among themselves over their own individual perceptions of the truth, when we, who possess the daily opportunity of studying and treating mankind “whole,” persist in seeing him only as an animal, and relegate to others—or completely ignore—that vast and mysterious region whereon the emotions, thoughts and volitions play their tremendous roles?

## REVIEWS.

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CLIO MEDICA VOL. V. PHYSIOLOGY. By JOHN F. FULTON, M.D., Sterling Professor of Physiology, Yale University. Pp. 141; illustrated. New York: Paul B. Hoeber, Inc., 1931. Price, \$1.50.

THIS small volume supplies a very useful summary of the history of physiology. It groups the discussion according to several of the major subjects of physiologic study, and this assists the reader to obtain a clear picture. The earlier studies of the circulation of Fabricius, Sarpi, and Caesalpinus which later reached fruition in Harvey's work are well described and enable one to see the familiar picture of the gradual evolution of knowledge. Interesting sections are devoted to the rise of the teaching laboratories, and the development of the American school. It is somewhat disappointing to find the field of neurologic investigations mainly neglected, but presumably the author considered that he had dealt with this aspect sufficiently in his other books. An interesting bibliography of articles of an historical character is appended. H. B.

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ARTERIAL HYPERTENSION. By EDWARD J. STIEGLITZ, M.S., M.D., Assistant Clinical Professor of Medicine, Rush Medical College, University of Chicago. Foreword by ROLLIN T. WOODYATT, M.D., Clinical Professor of Medicine, Rush Medical College, University of Chicago. Pp. 280; 21 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, \$5.50.

THE author gives some interesting and original views which may, as Dr. Woodyatt suggests in his Foreword, be entitled to serious study. This should, however, decidedly precede their acceptance. Briefly stated, the pathogenesis of hypertension is explained as follows: irritation of arteriolar musculature by various sorts of stimuli (concerning which the author holds an enviable certainty of knowledge); irritation which leads to spasticity and continuous increased muscle tone, resulting in muscular fatigue, consequent muscular hyperirritability and more spasticity (so that the hypertension may automatically persist even after original stimuli have

ceased to act!), with eventually muscular exhaustion and degeneration, replacement fibrosis and a terminal arteriolar sclerosis. He condemns the use of iodids in treatment, but claims excellent results from bismuth subnitrate. As regards renal function, he champions the theory of a secretory activity of tubular epithelium.

R. K.

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THE PAPYRUS EBERS. Translated from the German Version by CYRIL P. BRYAN, M.B., B.Ch., B.A.O., Demonstrator in Anatomy University College, London, With an Introduction by PROFESSOR G. ELLIOTT SMITH, M.D., D.Sc., Litt.D., F.R.C.P., F.R.S., Professor of Anatomy, University College, London. Pp. 167; illustrated. London: Geoffrey Bles, 1930. Price, 10s. 6d.

A WELCOME companion to Breasted's recent sumptuous presentation of the Smith Papyrus (reviewed in these columns, 1931, 181, 129) is this description and translation of abstracts from the "longest and most famous of the documents relating to the ancient practice of medicine." Dating from the same approximate age as the Smith Papyrus, and like it presenting the records of an older folklore, these miscellaneous notes present an invaluable picture of the therapy of the ancient Egyptians with sidelights on their physiology, symptomatology and diagnosis. And yet, this book with translations from Joachim's German version, is the first of its kind in English. The author's pleasant, at times even breezy, style should help popularize an entrancing subject. A 35-page introduction by Elliott Smith gives some interesting firsthand illustrations of the problems of medical Egyptology and how they are often satisfactorily solved.

E. K.

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ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY, VOL. VI. THE PATHOGENIC STREPTOCOCCI, MONOGRAPH XI. THE RÔLE OF THE STREPTOCOCCI IN SCARLET FEVER. By DAVID THOMSON, O.B.E., M.B., Ch.B. (Edin.), D.P.H. (Camb.), Hon. Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London, and ROBERT THOMSON, M.B., Ch.B. (Edin.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 470; illustrated. Baltimore: The Williams & Wilkins Co., 1930.

VOLUME VI of these Annals is devoted to the Rôle of the Streptococci in Scarlet Fever. The entire volume is given up to Monograph XI of this series of research studies. So rapidly has research work on Scarlet Fever been carried out, particularly during the last five years since the discovery of the Dick toxin, that about 1400 research papers are referred to in this volume. The information obtained is



enormous and quite varied. A very careful and profuse index is supplied, making this information quickly accessible.

About fifteen different proofs are offered showing that Scarlet Fever is caused by a specific hemolytic streptococcus which may be justly called the *Streptococcus scarlatinae*. Attention is called to carbohydrate fermentation tests, the litmus test and the iodine test as dependable ways of differentiating various species of the hemolytic streptococci.

A most valuable aid to the research worker is presented in 13 full page illustrative plates which contain over 100 very exceptional photomicrographs. This volume, with volumes III, IV and V (published) and volume VII (to be published), represents an encyclopedia of information on the streptococci and the part they play in human and animal diseases. They cannot fail to be of great service to the future research worker in that they present the present state of human knowledge on the subject, and they will therefore form the basis of further researches for years to come.

W. K.

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OUTLINES OF MODERN BIOLOGY. By CHARLES ROBERT PLUNKETT, Associate Professor of Biology, New York University. Pp. 711; 198 illustrations. New York: Henry Holt & Co., 1930. Price, \$3.75.

THE outgrowth of photostated notes for a course in biology at Washington Square College, this book attempts the ambitious program of explaining as well as describing biologic phenomena on the concept of the living organism as a physicochemical mechanism. Protoplasm, nutrition, response, reproduction and evolution are discussed in necessarily elementary but admirably modern form, and without attaining simplicity at the price of superficiality. Three useful appendices offer a short classification of organisms, and of chemical compound symbols and nomenclature and a compact bibliography. It is the best of such textbooks that the Reviewer has had the fortune to meet and can be warmly recommended for medical as well as college scientific libraries.

E. K.

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A SYSTEM OF BACTERIOLOGY IN RELATION TO MEDICINE. VOL. II: COCCI, HEMOPHILIC BACTERIA. By Various Authors. Pp. 420. London: Medical Research Council, 1929. Price, £1.1.9 for this volume; for set, £8.14.9. Obtainable in the United States at British Library of Information, 5 East 45th Street, New York City.

FAVORABLE reviews of several volumes of the System of Bacteriology already have appeared in this JOURNAL. The present volume is

of similar character. Chapter I treats the staphylococci under the following headings: History, Morphology, Biochemical Reactions, Vitality, Distribution, Pathogenicity, Resistance, Classification and Treatment. Subsequent chapters are devoted to the Streptococci, the Pneumococcus, the Gonococcus, the Meningococcus, the Influenza Group of Bacteria, including *Bacillus Influenzæ*, *Bacillus Koch-Weeks*, *Bacillus Hæmoglobinophilus Canis*, *Bacillus Parainfluenzæ* and *Bacterium Pneumosintes*. Each of these chapters discusses at even greater length the morphologic, biologic and serologic characteristics of the various organisms. Special attention is paid to their pathogenic action and to methods of treatment.

The volume is more a discussion of the biologic and pathologic significance of the various organisms than a key for their identification and labelling with distinctive names. It furnishes a good exposition of the present-day knowledge of these organisms and their known or supposed relation to various diseases. An extensive bibliography appears after each chapter. The absence of an index is regrettable.

G. R.

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A SYSTEM OF BACTERIOLOGY IN RELATION TO MEDICINE. By Various Authors. Vol. V. Glanders, Diphtheria, Tuberculosis, Leprosy, Brucella, Anthrax. Pp. 505. London: Medical Research Council, 1930. Obtainable in the United States at the British Library of Information, 5 East 45th St., New York. Price, £1/1/9; for the set £8/14/9.

THOSE who have been accustomed to struggle with numerous books in various languages in order to learn what is known of an important infectious disease, cannot but welcome a work to which he can turn in the full confidence that if he desire to inform himself concerning one of the subjects listed, he will find it adequately treated. The topics are presented from every important standpoint—historic, geographic, etiologic, morbid anatomic, histopathologic, micro-bacteriologic, micro-chemical, diagnostic, prognostic, immunologic, therapeutic, prophylactic and preventative.

It is true that the space allotted to each is necessarily limited, making it impossible for it to contain a complete review of the literature; but it does in each case give the facts omitting the theories and fancies popular in the past but better forgotten in the present. This is a rare virtue, for scientific literature is burdened with reiterated error and obsolescent theory appearing again and again in slavish conformity to the conception that no presentation can be satisfactory unless the entire antecedent literature be completely reviewed.

An American reader will scarcely escape the impression that his fellow countrymen have received less than their due share of recognition either in the text or in the references.

For example it seems to the Reviewer that Opie's work upon juvenile tuberculosis which seems to have been overlooked, deserved extended mention. It is also, perhaps, to be regretted that the volume contains no index of its own.

J. McF.

THE SIGNIFICANCE OF THE PEKING MAN. By PROF. G. ELIOT SMITH, M.A., M.D., D.Sc., Litt.D., F.R.S. The Henderson Trust Lectures, No. XI. Pp. 20; 16 illustrations. Edinburgh: Oliver and Boyd, 1931. Price, Sixpence.

THIS lecture recently delivered at Edinburgh University by one of the most eminent authorities on human craniology tells the story of this most important discovery about primitive man in the author's usual clear and convincing manner.

E. K.

THE PAPERS AND SPEECHES OF JOHN CHALMERS DA COSTA, M.D., LL.D., Samuel D. Gross Professor of Surgery at the Jefferson Medical College, Philadelphia. Pp. 440; 7 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, \$6.50.

ONE of the most compelling, vivid and original and, if need be, caustic orators that medical Philadelphia has had the fortune to listen to in this generation has collected twenty-one of his papers and speeches for our edification. Dealing with the past and future of medicine, more than with the present, the book combines the wit of the *bonraconteur* with the vision of the prophet. As an instance of the former, he speaks of the Old Blockley Hospital, which was a striking example of the errors of municipal politics, "as reeling down the editorial pages of the newspapers." The Blockley politician believed in "*Lucrum Gaudium*"—the mosaic motto of the Pompeian house—"Gain is pure joy." He spoke of "snivel service reform." "He resembled a corkscrew in the fact that the more crooked he was, the more pull he had . . . he was apt to boast that whisky never gave him a head, which only goes to prove that whisky is not more powerful than the Almighty; . . . his parents were poor but Irish; he kept his party faith and everything else he could get his hands on" and so on through many lusty pages. In an essay on the surgeon he says: "A surgeon is like a postage stamp. He is useless when stuck on himself. A vain surgeon is like a milking stool; of no use except when sat upon. I don't see how any real surgeon can be vain. He is too often near to the inscrutable mystery of death—he sees too often the weaknesses of men—he too often stands at cross roads of judgment, knows that one way is the wrong way, but finds no sign to mark it—he too often

has to reproach himself for mistakes—he too often sees calamity tread on the heels of calamity—he too often laments, impotent to save, and watches ‘Beauty and anguish walking hand and hand, the downward way to death.’”

Not only are home truths emphasized with the light rapier thrust, but artistic heights of description are reached (as in “Dickens’ Doctors”); intimate biographies sketched (Larrey, Gross, Long, W. W. Keen, Pepys) and trenchant estimates made of the good and bad in our present medical tendencies. Truly a keen observer of men and deeds.

E. K.

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PRACTICAL RADIATION THERAPY. By IRA I. KAPLAN, B.S., M.D., Director, Division of Cancer, Department of Hospitals, New York City; with a special chapter on Applied X-ray Physics by CARL B. BRAESTRUP, B.Sc., P.E., Radiation Physicist, Division of Cancer, Department of Hospitals, New York City. Pp. 354; 225 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, \$6.00.

THIS book offers a description of radiation therapy as practised at Bellevue Hospital. The book consists of 12 chapters. One hundred and twenty-nine pages are concerned with equipment and Roentgen ray physics, 16 pages on nursing care and organization and the remainder on the practical application of Roentgen and radium therapy and endothermy. The book is arranged very much like notes from which one would give didactic lectures; for instance, a picture of a case is shown on one page and on the opposite page the treatment employed is detailed. The book is presumably planned so that those who wish to begin Roentgen and radium therapy can refer to it and possibly obtain information as to the precise treatment employed in a given case. In many conditions the knowledge of the condition and the technique of practical radiation must be assumed, as the author discusses them very briefly.

E. P.

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PRACTICAL TREATISE ON DISEASES OF THE DIGESTIVE SYSTEM. Vols. I and II. By L. WINFIELD KOHN, M.D., F.A.C.P. Pp. 1125; 542 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, \$12.00.

IF the purpose of this text is to present the established knowledge of the gastrointestinal tract, it is well fulfilled by the author. The book is in general well written and thoroughly sound. It gives full information of the textbook type and displays practical good judgment in diagnosis and treatment. In the latter there are included a wide variety of measures discretely recommended and without the fads that too often mar writings on gastroenterology.

It is difficult to criticize adversely a book in which the essentials are well presented, but after this is said the Reviewer cannot see that it adds much to the subject. It seems to fail in this in general, although no individual section is especially deficient. One reason for this may be that the work represents an effort to integrate the entire gastrointestinal tract on the basis of normal and pathologic physiology. The numerous chapters on general considerations, of which that on physiology is very good, are the means of doing this, and they give a comprehensive idea of the factors underlying the behavior of the digestive system. This has resulted in a scattering and repetition of much of the information about a given topic with consequent incompleteness and confusion. In such a brief review it has not been possible to go into details, and it can only be stated that, although there is nothing to be condemned, the work lacks that keenness of selection and presentation which marks a great text.

F. L.

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BIOASSAYS—a HANDBOOK OF QUANTITATIVE PHARMACOLOGY. By JAMES C. MUNCH, Director of Pharmacologic Research, Sharp and Dohme; Pharmacologist, Bureau of Biologic Survey, United States Dept. of Agr. Pp. 958; 22 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, \$10.00.

THIS is an exhaustive—and somewhat exhausting—compilation of the literature dealing with the methods of pharmacodynamics, their application to the quantitative testing of drugs (including vitamins) and the results obtained, the latter including 239 tables. Chemical methods are also presented in some cases (notably digitalis and ergot) but not in all. A brief chapter on the statistical interpretation of results is included. The author's primary purpose is stated to be the avoidance of unnecessary duplication of effort along these lines by making available under a single cover a record of what has already been done: the references cited total 6183. It is perhaps inevitable that even this impressive number is far from complete, not only with regard to the quantitative action of drugs, but also with regard to methods, but the book contains a tremendous amount of useful information.

C. S.

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PROTEUS, BAND I. VERHANDLUNGSBERICHTE DER RHEINISCHEN GESELLSCHAFT FÜR GESCHICHTE DER NATURWISSENSCHAFT, MEDIZIN UND TECHNIK, MIT FESTGABE FÜR WILHELM HABERLING. By PAUL DIERGART. Pp. 281. Bonn: Bonner Druck- und Verlagsanstalt, L. Neuendorff, 1931.

BEARING the same name as a similar periodical from the Rhine region, defunct for over a century, this interesting volume combines

the post-war *Proceedings* of the Rheinisch Natural and Medical History Society with a Festschrift for Wilhelm Haberling on the occasion of his sixtieth birthday. It is not entirely clear whether it is an "occasional" volume or the first of another periodical on the History of Science. The excellence of its contents makes one hope for the latter. In addition to the special Fest articles, the volume contains lists of numbers and of programs and numerous abstracts of presentations.

E. K.

QUANTITATIVE CLINICAL CHEMISTRY, VOL. I—INTERPRETATIONS.

By JOHN P. PETERS, M.D., M.A., Professor of Internal Medicine, Yale University School of Medicine, and DONALD D. VAN SLYKE, PH.D., SC.D., Member of The Rockefeller Institute for Medical Research. Pp. 1264; 124 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, \$12.00.

THE rapid growth of our knowledge of biochemistry in the present century and the successful application of much of it to the needs of clinical medicine has rendered an adequate presentation of the subject in book form increasingly desirable and increasingly difficult. The present volume is a successful treatment of the subject in a comprehensive manner—as might be predicted when the names of the authors are considered—and far removed in aim and scope from the ordinary handbook of clinical laboratory methods. Though the book was outlined 6 years ago along more conventional lines, it was fortunately recognized in time that normal physiological values and variations and an adequate discussion of the causes and mechanisms were necessary for an intelligent presentation. Not only did this prove so bulky that a second volume on methods was necessitated, but even this first reference book has devoted more space to the physiological sections than the clinical.

Of the 21 chapters, the lengthiest is that on acid-base balance (151 pages) with carbohydrate metabolism a close second (148 pages), and the chapter on hemoglobin third (135 pages). The chemistry of the proteins has been divided into 6 chapters which together total over 200 pages. The remaining third of the pages covers total metabolism; lipoids; organic acids and ketones; phenols; blood volume; and the chief bases and acid radicles. To attempt to evaluate all sections of such a comprehensive work would be impossible in a short review and often impertinent. One need have no hesitation, however, in recommending it as an authoritative and accurate statement. The references, too, at the end of each chapter are copious; for instance, there are 323 references to the chapter on hemoglobin, alone. They are of high grade, though disproportionately restricted in source.

The treatise illustrates in a sterling manner the application of biochemistry, physiologic as well as pathologic, to medicine. The

physician and the worker in the preclinical sciences will find it a well balanced and thoroughly modern discussion of the thousand and one chemical questions that today enter in the study of the normal or the diseased individual. The scope of the treatise may be gathered from citing the subheadings of one of the shorter chapters (on lipoids); nature, distribution and function of lipoids; fats; lipids; cholesterol; the metabolism of the lipoids; digestion, absorption and oxidation; the synthesis of lipoids; the excretion of lipoids; abnormal accumulation of lipoids in the body; the nature and concentration of the lipoids in blood; the blood lipoids in disease.

While the older fashioned clinician will doubtless be somewhat appalled at this presentation of one phase of what is now included in "Clinical Medicine," the book will be of immense value to those "internists" endeavoring to keep on the crest of the wave of the latest developments of scientific clinical medicine or to conduct investigations suitable for presentation at the most advanced clinical meetings.

B. L. and E. K.

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DISEASES OF CHILDREN. By BRUCE WILLIAMSON, M.D., Edin., M.C.R.P., Lond., Physician to the Royal Northern Hospital, London. Pp. 290; 50 illustrations. New York: William Wood & Co., 1931. Price, \$3.50.

THIS is a limp leather, pocket-size manual for students. In condensing the subject of pediatrics into 290 pages, completeness has been sacrificed to brevity. Especially is this noticeable in the field of treatment, where specificity is not only desirable but essential to the beginner. From a diagnostic point, the book is more useful as the list of disorders is complete and the description of them clear. The author has arranged diseases according to their importance and frequency in general experience. This gives the book sound practical value, as subjects of purely academic interest are avoided. A feature which appeals to the reviewer is a short exposition of the normal prefacing each chapter.

J. S.

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SOME ASPECTS OF THE CANCER PROBLEM. Edited by W. BLAIR BELL, B.S., M.D. (LOND.), F.R.C.S. (ENG.), Hon. F.A.C.S., Fellow of King's College, London; Director of the Liverpool Medical Research Organization. Pp. 543; 273 illustrations. New York: William Wood & Co., 1930. Price, \$20.00.

GRANTED that the nature and control of cancer is one of, or perhaps *the* greatest of medical problems of the day, any honest and sustained attack from an intelligent point of view must be attentively considered. It is, therefore, profitable that the well-known

work of the author during the past 20 years should be assembled and published in book form, even though the high price and the necessarily tentative quality of its conclusions may restrict its widespread private sale.

The resemblance of chorionic epithelium to carcinoma and the growth-inhibiting and abortifacient action of lead suggested to the author the use of lead in the treatment of cancer. The true cures obtained in some proven cases of carcinoma and the improvement noted in others seemed to justify as complete as possible a study of this working hypothesis. These 543 pages, many leading into distant physicochemical fields, are the present result and the end is not yet.

Lest the reader feel that he has been left in the air, a general summary is offered, including the elucidation (?) of evidence along four lines: histologic, physicochemical, physiologic and toxicologic. Careful perusal leaves at least one reader in the position deprecated; but perhaps that is, after all, the proper position at the moment in regard to this complicated subject. E. K.

TEXTBOOK OF HUMAN EMBRYOLOGY. By CLEVELAND SYLVESTER SIMKINS, Associate Professor of Anatomy, University of Tennessee Medical School, Memphis. Pp. 469; 263 illustrations. Philadelphia: F. A. Davis & Co., 1931. Price, \$4.50.

THIS book considers the functional aspects of reproduction and of development, for the most part in the human, and is adapted for the use of medical students. The author has availed himself of the results of recent investigators, mostly of the last two decades. Where the illustrations are taken from original sources, as many of them are, the usual diagrammatic representations have been avoided. By assembling the information and illustrations in this manner the author has succeeded in presenting the contemporary viewpoint of the main facts of human embryology. A bibliography of 10 pages is included. W. A.

## BOOKS RECEIVED.

### NEW BOOKS.

*Adventures in Biophysics.* By A. V. HILL, Sc.D., LL.D., M.D., F.R.S., Foulerton Research Professor of the Royal Society. Pp. 162; illustrated. Philadelphia: University of Pennsylvania Press, 1931. Distributor: Charles C. Thomas, Springfield, Ill. Price, \$3.00.

*Progressive Medicine, Vol. II, June, 1931.* Edited by HOBART AMORY HARE, M.D., LL.D., Professor of Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College. Assisted by LEIGHTON F.



- APPLEMAN, M.D., Instructor in Therapeutics, Jefferson Medical College. Pp. 346; illustrated. Philadelphia: Lea & Febiger, 1931.
- Eye, Ear, Nose and Throat for Nurses.* By JAY G. ROBERTS, PH.G., M.D., F.A.C.S., Licentiate, American Board Otolaryngology. Pp. 213; 102 illustrations. Philadelphia: F. A. Davis Company, 1931. Price, \$2.25.
- Textbook of Histology.* By EUGENE C. PIETTE, M.D. Pp. 466; 277 illustrations. Philadelphia: F. A. Davis Company, 1931. Price, \$4.50.
- Nosokomeion (Quarterly Hospital Review), No. 2, April, 1931.* Pp. 434. Stuttgart: W. Kohlhammer. Price, R.M. 8.
- Illustrations of the Methods of Reasoning.* By DANIEL SOMMER ROBINSON, PH.D., Professor of Philosophy in Miami University. Pp. 346. New York: D. Appleton & Co., 1927. Price, \$2.00.
- Food Allergy.* By ALBERT H. ROWE, M.S., M.D., Lecturer in Medicine in the University of California Medical School, San Francisco. Pp. 442. Philadelphia: Lea & Febiger, 1931. Price, \$5.00.
- The History of Medicine.* By BERNARD DAWSON, M.D. (LOND.), F.R.C.S. (ENG.). Pp. 160; 31 illustrations. London: H. K. Lewis & Co., Ltd., 1931. Price, 7s 6d.
- Health on the Farm and in the Village.* By C. E. A. WINSLOW, DR.P.H., Professor of Public Health, Yale School of Medicine. Pp. 281; illustrated. New York: The Macmillan Company, 1931. Price, \$1.00.
- Guy's Hospital Reports, Vol. 81 (Vol. 2, Fourth Series), No. 2, April, 1931.* Edited by ARTHUR F. HURST, M.D., Assisted by various contributors. Pp. 126; 1 illustration. London: The Lancet, Ltd. Price, 12/6 net.
- Klinische Physiologie, Part 2.* By PROF. DR. BERNARD STUBER, Oberarzt der Medizinischen Klinik der Universität Freiburg i. Breisg. Pp. 142; 17 illustrations. München: J. F. Bergmann, 1927.
- The Infant Welfare Movement in the Eighteenth Century.* By ERNEST CAULFIELD, M.S., M.D. With a Foreword by GEORGE FREDERIC STILL, M.A., M.D. (CANTAB.), HON. LL.D. (EDIN.), F.R.C.P. (LOND.). Pp. 203; 8 illustrations. New York: Paul B. Hoeber, Inc., 1931. Price, \$2.00.
- A System of Bacteriology in Relation to Medicine. Vol. VIII. Fungi, Streptothricæ, Normal Flora, Swine Erysipelas.* By various authors. P. 389; illustrated. London: Medical Research Council, 1931. Price, £1.1.9 for this volume; for the set, £8.14.9. Obtainable in the United States at British Library of Information, 5 East 45th St., New York City.

## NEW EDITIONS.

- Resistance to Infectious Diseases.* By HANS ZINSSER, M.D., Professor of Bacteriology and Immunity, Medical School, Harvard University. Pp. 651; illustrated. Fourth edition completely revised and reset. New York: The Macmillan Company, 1931. Price, \$7.00.
- Diabetes, Its Treatment by Insulin and Diet.* By ORLANDO H. PETTY, A.M., M.D., F.A.C.P., Professor of Diseases of Metabolism, Graduate School of Medicine, University of Pennsylvania. With an Introductory Foreword by JOHN B. DEAVER, M.D. Pp. 231; 13 illustrations. Philadelphia, F. A. Davis Company, 1931. Price, \$2.00.

In this excellent book "the main object is the education of the diabetic in all matters pertaining to his health."

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

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**Some Lessons of the Distribution of Infectious Diseases in the Royal Navy.**—In the third Milroy lecture, Captain S. F. DUDLEY (*Lancet*, 1931, 220, 5613) brings out some interesting features concerning the epidemiology of undulant fever as a result of studies he has made on the old naval health reports of the British Navy. He notes that 100 years ago Malta was famous for its magnificent location, climate and freedom from disease; whereas 50 years later the British naval officer who was ordered to Malta went there with fear and trembling on account of the large number of cases of fever that occurred in that community. The fever rate had more than doubled from that of 50 years ago. In studying the influence of undulant fever on ships' crews, he notes that at this period the illness of the Mediterranean fleet as a result of febrile disorders had nearly trebled. It remained high until 1900, when the relationship between Brucella infection and goats led to the prohibition of the latters' milk in the Mediterranean fleet. Without discussing in detail this interesting lecture, Dudley points to several features which are of moment in his presentation. He thinks that after the undulant fever had been introduced into the ships as a result of the drinking of infected goats' milk, the infection may possibly have been transmitted directly from man to man. He holds that the disease evidently did not exist prior to 1860; otherwise it would not have escaped the notice of naval surgeons, and he substantiates this statement by referring to Theobald Smith's statement that the appearance of Br. abortus type of undulant fever prior to 1922 cannot be explained by the disease having escaped the notice of American physicians. More particularly is this point stressed in conjunction with the fact that since 1897 Br. abortus has been known to be present in cows' milk. It is suggested that the bovine type of brucella infection has increased its infectivity for man by passage through the pig or goat or that the present type of brucella infection may be derived from imported caprine strains. Some such condition must exist as in Porto Rico, where Br. abortus infection is extremely prevalent in cattle.

The strains isolated there are practically nonpathogenic to man. The author says that the recent types of brucella organism may be the development of passage through the host in which these organisms resided. It is quite possible that the present-day type of undulant fever may be due to the "attempt of an occasional parasite of man, which had wandered out of its specific host, the goat, to adapt itself to a purely human environment."

**Experimental Acute Glomerulitis.**—The reports of investigators attempting to produce glomerular nephritis in animals through the medium of injected bacteria with the products of their growth have been most contradictory, write LUKENS and LONGCOPE (*J. Exper. Med.*, 1931, 53, 511). They therefore devised a series of experiments to find out if an induced state of hypersensitiveness could be produced through material which might, when brought into concentrated form through contact with the renal circulation, produce some altered response of the kidney cells. Without going into the details of the experimental methods, suffice it to say that injections of killed hemolytic streptococci were made into the left renal artery, the contralateral kidney being used for control, and the animals were sensitized. Fifty-two rabbits were used; 23 were sensitized and 29 normal. They were killed at various times after the intra-arterial injection. In view of the fact that particulate matter was found in the small bloodvessels of the injected kidney, it was necessary further to control the experiment by the injection of inorganic matter in the form of a bismuth salt. Experiments proved that an acute glomerulitis resembling very closely certain types of glomerular nephritis in man might be brought about through the injection of suspension of killed streptococci. The histologic lesion produced consisted of hyalin thrombi in the capillaries, often with focal distribution, but at times so diffuse that nearly every glomerulus was involved. Glomerular changes consisted chiefly of necrosis and exudation, but there was also injury to the tubular endothelium and the interstitial tissue. The study of the sections suggests that the retention of clumps of dead streptococci in the capillaries of the glomerulus is the cause of the pathologic changes, but it is not mechanical, as the picture was not reproduced when bismuth was injected. The suggestion, therefore, is advanced that the presence of these bacterial bodies in the glomeruli is of extreme importance, particularly when occurring in the sensitized rabbit whose glomeruli are acted upon by the disintegrated products of the dead streptococci.

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## SURGERY

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UNDER THE CHARGE OF  
T. TURNER THOMAS, M.D.,  
PHILADELPHIA, PA.

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**Extravasation from the Ureter.**—GEISINGER (*Ann. Surg.*, 1931, 93, 544) state that extravasation from the ureter in the absence of external traumatism is an unusual lesion of grave significance, herewith exhib-

ited in 3 cases. In all 3 instances the causative factor apparently was neerosis from impaction of a calculus within the ureter. The clinical picture depends upon the amount of extravasation, the virulence of the associated organism and the tissue reactions of the patient. Rapidly spreading infection may result or the process may become localized, with or without abscess formation. The fact that one of the cases recovered entirely without operative intervention on the affected side, is interesting and suggestive. As a rule, however, the condition will be frankly surgical. The time for the application of this surgery and the type of operative procedure undertaken, will be dictated by the conditions obtaining in the individual case.

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**Peptic Ulcer.**—EMERGY and MONROE (*Am. J. Roent.*, 1931, 25, 51) say that a study has been made of the value of the Roentgen ray to the clinician in following the treatment of patients with ulcer of the stomach or duodenum. The accuracy of the Roentgen examination is shown to be high as compared with most kinds of laboratory procedures. However, it is a mistake for clinicians to place implicit confidence in the results of the Roentgen findings and to discard entirely the older methods of investigation. It was found that a correct diagnosis was reached in 93 per cent of those patients having an ulcer. Retention as shown by Roentgen examination was found to give a true picture of clinical retention in 67 per cent of cases. The presence or absence of tenderness over an ulcer was found to have no clinical value. A study of the Roentgen findings and the clinical symptoms shows that it is not possible to diagnose a healed duodenal ulcer by the Roentgen ray. Moreover, the data support the idea that duodenal ulcer is a chronic disease which is rarely cured by treatment (medical).

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**Acute Intestinal Obstruction.**—OCHSNER (*Surg., Gynec. and Obst.*, 1931, 52, 702) says that in all cases of ileus there are varying degrees of vascular occlusion. The prognosis in ileus depends upon the length of time which has elapsed since the onset, the location of the obstruction and the previous therapy. Blood chemistry determinations are of value for prognosis and proper treatment. Symptoms and signs of ileus are usually characteristic. Plain roentgenograms of the abdomen with the patient in the upright position without the administration of contrast media are of value in diagnosing ileus. Early operation or relief of obstruction in ileus is imperative. Enterostomy is of value in both the adynamic and obstructive types of ileus, provided enterostomy alone is not employed. Splanchnic block, preferably by means of splanchnic analgesia (Koppis) is of distinct value in adynamic ileus. Drugs are of little, or no value, in the treatment of ileus.

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**Studies on High Intestinal Obstruction.**—ARMOUR, BROWN, DUNLOP MITCHELL, SEARLES and STEWART (*Brit. J. Surg.*, 1931, 18, 467) state that death in untreated cases of high intestinal obstruction is preceded by the progressive development of severe alkalosis, by gross lowering of the blood chlorid and at the last, by an increase in the blood urea. For some days before death, the urine is chlorid free and the stomach contents contain no free hydrochloric acid, though their total chlorid

content is normal. It is immaterial whether the bile and pancreatic juice enter the intestine above or below the obstruction. The time of survival is greater the lower the obstruction. Administration of both chlorid and water below the obstruction causes the chemistry of the blood, urine and stomach contents to remain normal and also greatly prolong life. Death ensues only after some four weeks and cannot be attributed directly to the obstruction. With peptone and carbohydrate added to the chlorid and water, life can be prolonged for seven weeks or more. Withdrawal of the chlorid then brings about death with the usual clinical and chemical symptoms. The occurrence of *Bacillus welchii* in the stomach contents is the same in treated and untreated animals. It is concluded that death is due not to toxemia, but to the clinical changes following the loss of chlorid and water and is prevented by their supply. Treatment therefore consists in supplying chlorid and water until continuity of the intestinal canal has been reestablished. There is no evidence that excessive breakdown of tissue protein is an essential accompaniment of high intestinal obstruction.

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## THERAPEUTICS

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**Paravertebral Alcohol Injections in Angina Pectoris.**—This procedure has been employed extensively by PLETNEW (*Zeitschr. f. Kreislauf-forsch.*, 1931, 23, 177), who reports upon the duration of the results obtained. Pletnew believes this method to be far preferable to the various operative procedures upon the ganglia and vegetative nerves because it is generally equally effective and because the operative procedures are associated with 12 to 18 per cent of immediate mortality. To secure lasting results Pletnew finds it necessary to make systematic repeated injections of 5 cc. of a 1 per cent novocain solution in the region of each ganglion, followed a few minutes later by 5 cc. of 70 to 80 per cent of alcohol. Such injections should be repeated weekly. Before the injection the patient should be prepared by receiving a hypnotic on the preceding evening and a dose of morphin or pantopon 2 hours before the treatment. No ill effects have followed this procedure except in rare instances where the alcohol has apparently been injected directly into the ganglion, rather than into its immediate neighborhood. In such cases an immediate attack of anginal pain has been induced, but it has passed off promptly. In view of the latter occurrences Pletnew believes it possible that fatal accidents may occur

from such injections, but he has not seen any. By means of these repeated efforts chemically to cut the nerve connections between the heart and spinal cord he has obtained satisfactory lasting results in 3 of 22 cases; fairly lasting results in the majority of the remainder and has met with total failure in only 2 cases, in both of whom sympathetic nerve operations were subsequently necessary.

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**Rather Rare Toxic Manifestations of Tobacco.**—The majority of the toxic effects of tobacco are acute and disappear promptly with cessation of the use of nicotine. LIPPMANN (*Klin. Wchnschr.*, 1931, 10, 169) reports certain rather rare but more serious effects. The appearance of angina in a group of smokers is probably due to the vasoconstrictor effect of nicotine on the coronary arteries. Cases are reported in which repeated omission and resumption of smoking resulted in the disappearance and recurrence of the angina respectively. It is suggestive that in some cases nicotine may cause elevation of the blood pressure. Smoking is occasionally responsible for pain over the extremities. The vascular spasm responsible for the pain disappears often only after the complete exclusion of tobacco. Chronic intestinal symptoms, such as constipation and cramps are noted among rather young smokers.

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**Insulin-sensitive and Insulin-resistant Diabetes.**—That certain complications of diabetes mellitus are associated with a decrease of the beneficial effect of insulin is well recognized. FALTA and BOLLER (*Klin. Wchnschr.*, 1931, 10, 438) now call attention to the group of cases which exhibit insulin resistance regularly without the presence of complications. The pathology present in this group is varied. Most frequently there exist endocrine imbalance, liver disease, encephalitis and psychic disorders. The authors describe test methods which allow the estimation of the degree of resistance. In applying these one finds relative insulin resistance surprisingly often. Of a group of 74 patients, 52 showed some degree of insulin resistance. In general, resistance is more apt to be present among elderly individuals with obesity or arterial hypertension. The authors conclude that human diabetes mellitus cannot always be explained by an insufficient functioning of the islands of Langerhans.

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## PEDIATRICS

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UNDER THE CHARGE OF

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**Tuberculosis in Infants and Children.**—HAMIL (*Am. J. Dis. Child.*, 1931, 41, 1023) states that the supravital test gives a simple and accurate method for the laboratory study of the white cells in any disease. Monocytes are increased above the normal figure in active tuberculosis.

This observation is constant in severe tuberculosis, and the modified type of this cell predominates in severe and terminal stages of the disease. This type of monocyte is found in the blood of patients who do not have tuberculosis and is therefore not pathognomonic of the disease in infants and children. The lymphocyte is the only type of cell in the circulating blood which appears to have a constant relation to the tuberculous process. The total lymphocyte count is decreased below the normal figures in all active types of tuberculosis, this decrease depending on the severity of the disease. The lymphocyte count is increased in the healing stage; the constancy of this increase depending on the progression of healing. The total white blood cells and total neutrophils are increased in the terminal stage of severe tuberculosis. An increase in neutrophils is not constant in cases with ulceration and the formation of abscesses. The ratio of monocytes to lymphocytes is increased in active tuberculosis, this increase depending on the severity of the disease. It is due to both an increase in total monocytes and a decrease in lymphocytes, the latter factor being the more constant. As healing occurs, there is a decrease in the ratio, which is fluctuant until the healing is well advanced. In cases with multiple lesions in different pathologic stages, no reliance can be placed on the monocyte-lymphocyte ratio to determine the status of the tuberculosis. The tuberculin skin test and treatment with ultraviolet light, in cases of chronic and advanced healing tuberculosis, cause a change in the monocyte-lymphocyte ratio, and blood studies should be interpreted in the light of such influencing factors. He suggests that fluctuations in the different types of white blood cells in the peripheral circulation of patients with tuberculosis are due to stimulation of the reticular cells to proliferation by products of the tubercle bacilli and the tuberculous lesions rather than either to the simple presence of tubercle bacilli in the body or to the demand for the different types of cells according to the type or stage of the pathologic lesion. The great value of the white cell picture in tuberculosis in children lies in the distinction between active severe tuberculosis or an early healing tuberculosis and an advanced healing or latent tuberculosis in the child who shows some of the clinical signs of tuberculosis but no definite symptoms by which to determine the status of the pathologic process. Many children are brought to the practitioner for examination solely on the history of contact with tuberculous patients. They may show only a positive tuberculin test, which in children is a significant sign, and perhaps a positive D'Espine sign or a suggestion of hilar or suprahilar shadow beyond the normal limits. In such a case, the symptoms may be slight and in any event variable, although the pathologic process may be relatively extensive and rapidly progressive. A study of the white cells in such a case and a comparison of the total figures for each cell type with the normal total figures, and a computation of the monocyte-lymphocyte ratios will aid in determining whether the child should be permitted the freedom of the home life, or whether it should be subjected to further observation under tuberculosis management. There is no constant observation in the study of the white cells in the peripheral blood of children with tuberculosis that would warrant a diagnosis of tuberculosis without the support of clinical evidence. By the use

of supravital technique, an accurate and thorough study can be made of the different types of white blood cells. The study of the total number of monocytes and the total number of lymphocytes can be made by a fixed smear equally as well.

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**Premature Infants.**—CRAWFORD (*Arch. Ped.*, 1931, 48, 293) presents a study made of 231 prematures seen in 4495 deliveries, which was an incidence of 5.2 per cent. The average mother of 21 years had 2 months prenatal care and 91.8 were in good health. The cause of prematurity was determined in 91 cases as follows: syphilis, 31; twins, 26; toxemia, 12; placenta previa, 5; and other lesser causes. The average birth weight was 4 pounds, with a loss of 7 ounces for the first 5 days. The birth weight was usually regained by 11 days, and on discharge upon the twenty-first day the weight averaged 4 pounds and 14 ounces. Gavage feeding was necessary in 17.4 per cent. Temperature was maintained in all cases by using a closed bed heated with electric lamps. Death occurred in 82 cases or 35.5 per cent and was due to the following causes: prematurity, 50 per cent; syphilis, 23.2 per cent; pulmonary infection, atelectasis and intracranial hemorrhage each 5 per cent.

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**Interpretation of Pain in Infancy.**—SHELDON (*Brit. Med. J.*, 1931, 1, 530) says that the commonest effect of pain on a baby is to make him cry, and he feels that much help is to be gained from a study of the characters of this expression. Pain is by no means the only cause of a baby's crying. Hunger, cold, soiled napkins, or simply a desire to be amused may be contributing factors. It is not until the child exercises his will that crying due to temper makes its appearance so that this cause of crying is exceptional under 6 months of age. The features that should always be noted the cry is intermittent or continuous; whether it is a piteous wailing or a short, sharp scream; and whether it occurs at any particular time of the day or night. It is important to know the relation to the ingestion of food, and whether it is relieved or aggravated by the ingestion of food. Belching of gas often relieves the crying. It may be that the disturbance occurs only after sucking, after micturition or after defecation. Under the stress of severe pain the infant may not cry because of holding his breath, as so often seen in severe colic. The posture during the attacks of pain is important. The hips may be flexed so the thighs are on the abdomen, while the arms may be bent, with the elbows firmly pressed against the sides. In other cases the infant may be extended rigidly, with arched back, so that he supports himself on his head and heels. In many instances with careful clinical examination areas of distinct tenderness associated with pain may indicate the localization of the pain.

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**The Simplified Treatment of Empyema in Children.**—NOEGGERATH (*Münch. Med. Wchnschr.*, 1931, 78, 303) has returned to the older method of treating this condition because in resection of ribs the prognosis is rather unfavorable, and because pleural puncture, whether done only once or whether repeated, brings unsatisfactory results, especially in young children. He recommends an intercostal pleurotomy with the knife. Drainage is effected by means of a rubber drain.



Simple suction is done by a double bandage with plenty of bandage material which can be replaced easily. Besides its simplicity the method has three advantages. For the patient it is advantageous because the child bears this slight intervention much better than repeated punctures and is not inconvenienced by the tubes of the ordinary suction method. The nursing is simpler because the tubes are not long ones that might be bent or torn out. The physician values the method because it is simple and does not require any special instrument. In comparison with other methods the therapeutic results of the pleurotomy with subsequent drainage are favorable especially in young children less than 2 or 3 years of age.

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## DERMATOLOGY AND SYPHILIS

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**Intradermal, Scratch, Indirect and Contact Tests in Dermatology.**—RAMIREZ and ELLER (*J. Am. Med. Assn.*, 1930, 95, 1080), report the comparative study of four types of sensitization tests on a series of 500 patients with dermatoses in whom the etiology was suspected to be of allergic origin. They conclude that: (1) The patch or contact method is superior to other methods in determining susceptibility to external irritants, especially those of nonprotein structure; (2) the intradermal method of testing is more sensitive than the scratch method but it is more apt to produce false local reactions as well as severe systemic reactions in the highly sensitive. It would seem advisable to use the scratch method first and check up with the intradermal; (3) the indirect test, using the Prausnitz and Küstner method of local passive transfer, is particularly useful in young children who will not tolerate a large series of tests as well as in patients with persistent hyperirritability of the skin or where a dermatosis is so generalized that direct testing is impracticable.

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**Toilet Water Dermatitis.**—LANE and STRAUSS (*J. Am. Med. Assn.*, 1930, 95, 717). The authors direct attention to the possible injury to the skin from the denaturants such as diethylphthalate and quinin hydrochlorid used in the preparation of toilet waters. They describe in detail a peculiar dermatosis which has frequently been recognized by Continental observers since first described in 1916. This condition is known as berlock dermatitis and is due to the application of eau de

cologne containing oil of bergamot particularly after the rather long exposure to sunlight often associated with sea bathing or after excessive exercise with profuse perspiration. Clinically the dermatosis is seen most commonly on the neck, chest, back and shoulders, and consists of an inflammatory zone ranging from mild erythema to wheals or even vesiculation followed by a bizarre pigmentation in streak formation with the greatest intensity of pigmentation at the lowest portion of the irregular downward extensions. The name berlock dermatitis indeed is derived from the fancied resemblance of the eruption to the pendants of a necklace or watch chain. The authors in closing mention the experimental attempts that are being made to produce pigmentation of depigmented skin, such as vitiligo, by the combination of an alcoholic solution of oil of bergamot and ultraviolet irradiation.

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## GYNECOLOGY AND OBSTETRICS

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**Irradiation of Uterine Cancer.**—A study of 417 cases of uterine cancer which were treated at the State Institute for the Study of Malignant Disease at Buffalo between January, 1919, and June, 1925, has been presented by SCHREINER and KRESS (*Am. J. Roentgenol.*, 1931, 25, 359). Using the Schmitz classification, which is now well known, they found that radium irradiation supplemented with roentgen irradiation gave the following results in the treatment of carcinoma of the cervix. Five-year cures were obtained in 65 per cent of group 1, 27.7 per cent of group 2, 13.2 per cent of group 3, 1.1 per cent of group 4 and 6.5 per cent of group 5. Combining groups 1 and 2, which were the operable cases, 20 out of 52, or 38.4 per cent, have been clinically well five years or more. Groups 1, 2 and 3 in which, at the time of admission, it was thought possible to effect a cure resulted in 37 out of 181, or 20.4 per cent, being clinically well five years or more. The primary mortality was less than 1 per cent including all cases. Twelve patients died in from one to four years from intercurrent disease, there being no evidence of recurrence of the cancer. They believe that no other treatment could possibly have given the palliative results which were obtained in many of the remainder of the cases. Fistulae occurred 26 times in the far-advanced cases in which re-irradiation was deemed advisable and this should be borne in mind in the treatment of such cases. Two bladder fistulae healed spontaneously. As a result of his extensive

observations on the lethal radiation dose for cancer cells and the technique of the combined radium and roentgen treatment of uterine cancer, SCHMITZ (*Am. J. Roentgenol.*, 1931, 25, 364) concludes that about one-half of the highly anaplastic cases, that is, transitional round and basal cell and true adenocarcinomas and solid adenocarcinomas will probably succumb to a radiation tissue dose of 2.5 skin erythema doses if they extend within a radius of 6 cm. from the cervical canal. About 40 per cent of adult squamous-cell carcinomas, malignant adenomas and papillary and gelatinous adenocarcinomas may be killed by a radiation dose of 4 to 5 skin erythema doses if contained within a radius of 3 cm. from the axis of the uterus. The good end results of radiation treatment might be improved if it became technically possible and safe to increase the applied dose either locally or by distant irradiations. He states that many factors must be considered, such as the maximal tolerance of normal cells to radiation, the influence of obliterating endarteritis on the normal tissue, the resistance of the ureters to radiation, the formation of heavy scar tissue and coexisting infections. Such research is tedious and requires a continual follow-up of the cases for many years, but Schmitz believes that the progress made along these lines augurs well for the future of radiation therapy.

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**Salpingostomy.**—Following a few years of primary enthusiasm, it became the fashion in this country to deem salpingostomy for the restoration of the tubal lumen as a useless operation. No doubt this attitude has been due to the paucity of favorable results which followed the operation as done in the American clinics. In Central Europe, however, this subject continues to receive considerable attention and favorable results are reported in an encouraging number of cases. It is possible that there are some details of technique which are practised there which are not observed as we do the operation and, therefore, we shall briefly review the paper of MATWEJEW (Zentralbl. f. Gynec., 1931, 55, 302), who believes that the operation has merit when properly performed on selected cases. In his technique the uterus and adnexa are first liberated from adhesions. If there is merely a simple closure of the tube, the fimbria are widely separated by a surgical forceps, the patulousness of the tube tested with a sound and the separated fimbria are sutured with three fine sutures in such a manner that the tubal mucosa is brought over the peritoneal aspect of the tube as much as possible and without injury to the delicate cells of the mucosa. If a hydrosalpinx is present, a healthy portion of the tube is selected and clamped and the tube separated  $\frac{1}{2}$  cm. medial to the clamp. Tincture of iodine is not applied in order to avoid any adhesive inflammation. The accompanying vessel is ligated and a new ostium is made on the healthy stump. He always adds a ventrosuspension of the uterus to the operation of salpingostomy and attributes much of his success to this point, since in this manner the tubes are held out of the pouch of Douglas and are not so apt to become entangled in new adhesions. In addition it is essential that tubal insufflation be performed periodically during the postoperative period in order to maintain the patulous condition of the lumen. The operation is absolutely contraindicated in the presence of acute inflammation.

## OPHTHALMOLOGY

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**Eye Observations in Epidemic Cerebrospinal Meningitis.**—LEWIS (*South. Med. J.*, 1931, 2, 101) reported 65 cases of meningococcal cerebrospinal meningitis examined during the course of an epidemic. He found eye changes in 49 per cent. In 13 of these, however, hyperemia of the disk and retina or engorgement of the retinal veins were the only abnormalities present. Definite lesions were observed in 29 per cent. Three cases developed paralytic convergent strabismus which persisted after recovery from the meningitis. The squint was found to have disappeared spontaneously in 2 of the patients who were reexamined at a later date. Transient iridoplegia was noted in 2 cases and papillitis was present in 3 cases. In 1 case with internal hydrocephalus and 3 to 4 diopters swelling of the disk and retinal hemorrhages, autopsy showed a massive fibrinopurulent exudate covering the entire chiasm and the cerebellum. Two patients developed sudden total blindness, with dilated, stiff pupils but without any visible changes in the fundus. One patient died without regaining vision and the other gradually regained ability to count fingers in one eye and normal central vision in the other with greatly contracted fields; later he showed descending optic atrophy. The most frequent complication was acute iridochoroiditis or endophthalmitis, which occurred in twelve eyes of 9 patients. The main presenting symptom was loss of vision. Vitreous exudate was the main objective finding and only slight or moderate ciliary injection was present. Treatment, including intensive serum therapy, had no effect. Permanent blindness resulted in all the eyes involved. Two of the cases developed orbital cellulitis with marked proptosis and exposure of the cornea. In 1 of these cases ulceration of the cornea with perforation necessitated enucleation. Of the 32 cases with eye changes, 7 died, giving a mortality lower than the general death rate during the epidemic. Of the patients who recovered, 5 were permanently blind in one eye and 3 in both eyes; in the 7 of these patients the blindness was due to endophthalmitis.

**The Clinical Significance of Retinal Arterial Changes and Retinitis in Cardiovascular Renal Disease.**—GIPNER (*New York State J. Med.*, 1930, 30, 961) calls attention to four types of sclerosis which may be differentiated in the retinal arteries: senile, secondary, primary and hypertension—and describes their points of difference. The component parts of the picture of retinitis in any type of cardiovascular renal disease are essentially the same, hemorrhages, cotton-wool patches,

serofibrinous exudation, edema-absorbing exudates and macular stars occur in both the hypertension and the nephritis groups. The differentiation of the retinitis of primary hypertension disease from that of primary nephritis depends mainly upon the recognition of the hypertension type of arteriosclerosis. Additional characteristics of the nephritis cases are anemia, more massive exudation, more complete macular stars and a greater tendency to retinal detachment. In certain cases of glomerulonephritis developing in the presence of previous hypertensive disease the associated retinitis will have features of both types. Within the hypertension group proper it is possible to distinguish three distinct grades of retinal changes which belong characteristically to three distinct types or grades of hypertension. Retinal arteriosclerosis, usually mild, without retinitis occurs in mild benign hypertension. When cotton-wool patches and hemorrhages are seen in addition to the arteriosclerosis the case should be considered to be of severe benign type. While these patients usually have a relatively high diastolic pressure with some damage to the heart, brain or kidneys, their prognosis is fair under proper management. The presence of well-defined edema of the disks in association with sclerosis, hemorrhages and exudates is characteristic of the retinitis of malignant hypertension. In these cases, as in the retinitis of chronic glomerulonephritis, the prognosis is poor. The average length of life is less than 2 years. Some patients with retinitis of malignant hypertension type die from cardiac or cerebral complications while renal function is still adequate. Others go on to terminal renal insufficiency. In patients with retinitis of nephritis terminal renal insufficiency is always present.

**Chiasmal Syndrome Produced by Chronic Local Arachnoiditis.**—CRAIG and LILLIE (*Arch. Ophthalm.*, 1931, 5, 558) observed in 7 cases with syndromes suggesting tumor in the region of the chiasm, and in 1 case with a basofrontal syndrome that operation revealed chronic local arachnoiditis without adjacent or associated tumor. The diagnosis at operation was confirmed by necropsy in 3 cases. In the chiasmal group bitemporal hemianopsia for form and colors was present in 3 cases, bitemporal hemianopsia for colors in 1, homonymous hemianopsia for colors in 1 and partial homonymous hemianopsia with bilateral cecocentral scotomas in 1. The fundi were normal in 3 cases. The optic disks were pale in 2 cases and atrophic in 2. One case showed definite evidences of hypophyseal dysfunction. The sella turcica was normal in all cases. Improvement of vision occurred in 2 of the 4 patients who survived operation. In the case classified as a basofrontal syndrome examination revealed right nasal hemianopsia bilateral choked disks and a normal sella turcica. Fundus and fields returned to normal after operation. The authors feel that chronic local arachnoiditis affecting the optic chiasm is a definite clinical entity which cannot always be differentiated before operation from pituitary tumor, craniopharyngeal pouch cysts, glioma of the chiasm, aneurysm or suprasellar meningioma. Operation is justified in the inflammatory group even if the diagnosis is made prior to operation, since freeing the adhesions around the chiasm and optic nerves and allowing the encysted fluid to escape will often check the progress of the condition or alleviate the symptoms.

## RADIOLOGY

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**Conditions Commonly Called Colitis.**—The word "colitis" has frequently been used to describe various types of intestinal dysfunction in which there is no demonstrable organic disease of the large intestine. BARGEN (*Am. J. Roent. and Rad. Therap.*, 1931, 25, 308) protests against such misuse of the term. In cases of suspected intestinal disease painstaking and detailed anamnesis is of first importance. When discomfort or pain is present in the lower part of the abdomen the possibility of some disorder of the colon requires consideration. A regular routine of objective investigations is of great value in determining the presence or absence of disease. Roentgenologic studies have value in excluding from consideration intestinal neurosis which may be expressed in the conditions known as mucous colitis, spastic colitis and irritable colon. Colitis is an inflammatory disease of the colon and should not be diagnosed until thorough investigation has shown that inflammation, nothing less and nothing more, is present. Some other term, suggestive of part of a general bodily state, perhaps irritable colon, should designate the noninflammatory colonic disorders.

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**Uterine Hemorrhage Without Demonstrable Pathology.**—Chronic uterine hemorrhage occurring in women without demonstrable pelvic disease is a common condition, according to MARTIN (*Am. J. Roent. and Rad. Therap.*, 1931, 25, 349). Experimental evidence and operative material indicate that the etiologic factor is some abnormality of the endocrine system. An artificial menopause produced by radiation therapy, coupled with an anemia diet and iron medication, brings about excellent results in women over 40 years of age. In younger women a return to normal health is usually obtained through a combination of a small dose of intrauterine radium with Roentgen irradiation of the pituitary, an anemia diet, an iron tonic, an improved mode of living and the administration of glandular products.

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**Treatment of Tumors of the Bladder.**—In the opinion of COLSTON (*Am. J. Roent. and Rad. Therap.*, 1931, 25, 375) the presence or absence of infiltration is the most important factor to be determined before deciding on the treatment to be instituted. A careful cystoscopic examination is the most accurate method which we have at our disposal to determine this point. Noninfiltrating tumors are best treated by a combination of endovesical electrotherapy and direct radium application. By direct application of radium resistant tumors can usually be

made to respond promptly to the high-frequency spark and the chances of recurrence are markedly diminished. Infiltrating tumors should be treated by resection whenever this procedure can be safely carried out. When resection is impossible the tumor should be destroyed by diathermy through the open bladder and radium seeds implanted throughout its base. The intelligent treatment of bladder tumors can only be carried out by a combination of long experience with cystoscopic and electrotherapeutic methods, thorough knowledge of the technique of application and therapeutic results of radium and deep Roentgen therapy and thorough surgical experience in the treatment of these growths.

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**Urinary Tract Roentgenography by Means of Skiodan.**—Urography after the administration of skiodan was successful in 7 out of 8 cases examined by OCHSNER and WISHARD (*Am. J. Roent. and Rad. Therap.*, 1931, 25, 314), and the one failure was due to mechanical difficulties which prolonged the time of administration unduly. Tuberculosis, hydronephrosis and hypernephroma were among the lesions diagnosed. The writers agree with Beer, that the field for intravenous pyelography is much larger than the field for ordinary pyelography, but the former probably cannot completely supplant the latter.

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**The Postoperative Behavior of the Diaphragm.**—Before and after a variety of abdominal operations, high and low, the behavior of the diaphragm was investigated by ALLEN (*Radiology*, 1931, 16, 492). In 36 of the 94 cases studied the right diaphragm on the day after operation was sharply arched and high, and in 5 cases the left diaphragm was similarly affected, but in neither group was there roentgenologic or clinical evidence of disease in the corresponding lung. In some instances the affected dome was still high 3 weeks later, but a few subsided markedly after 3 or 4 days. The immediate cause of the condition is undetermined, but may be due to paralysis. In 57 per cent of the 94 cases both diaphragmatic arches were elevated, from causes which were more obvious and which apparently do not include paralysis. Both phenomena, but especially the unilateral high diaphragm, deserve attention, as the heart assumes a horizontal position suggesting displacement to one side or the other, and this, combined with a high position of one dome, may give an erroneous impression that atelectasis is present.

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**Endothelial Myeloma, or Ewing's Sarcoma.**—Endothelial myeloma, or Ewing's sarcoma, while usually the most malignant of all types of bone tumor, is highly radiosensitive and very responsive to the toxins of erysipelas and *Bacillus prodigiosus*, according to COLEY (*Radiology*, 1931, 16, 627). For this reason conservative treatment is justified for a limited period before resorting to amputation. Although many cases have been treated by radiation alone, or surgery and radiation, only one 5-year cure has been reported, and in this case no microscopic examination was made to verify the diagnosis. Treatment with the toxins of erysipelas and *Bacillus prodigiosus*, combined with radiation, preferably the radium pack, seems to be the best method of treating a primary operable case of endothelioma of the long bones. If the condition has

not shown improvement after 6 or 8 weeks, amputation followed by prolonged prophylactic toxin treatment should be considered. The author cites among inoperable cases 4 treated with toxins alone and 5 with toxins and radiation, all of which recovered and remained well for 5 years. Therefore, he thinks that few cases should be considered hopeless until such treatment has been tried.

#### Studies of the Effect of Roentgen-rays on the Healing of Wounds.—

POHLE, RITCHIE and WRIGHT (*Radiology*, 1931, 16, 445) exposed two groups of white rats to two qualities of Roentgen rays, preceding or following incisions in the skin. It was found that irradiation with either quality of the rays, in a dose of 1000 r at one sitting, from 1 to 30 days before the incision, did not affect the healing process perceptibly. Irradiation with a dose of 1000 r, with rays of either quality, immediately, 24 hours and 48 hours, respectively, after the incision, retarded the healing process, particularly in the 24-hour group, but did not interfere with the final formation of a smooth scar.

**Skin Malignancy.**—STEVENS (*Radiology*, 1931, 16, 435) holds that local cures of cancer of the skin by modern expert radiation should approach closely to 100 per cent. The great importance of biopsy for diagnosis and the selection of treatment is emphasized. Biopsies, he thinks, are perhaps more safely performed with the radio knife than with the cold knife, especially when melanomas and moles are concerned. In general, he regards radiation and electric surgery as of greater value in the treatment of cutaneous malignant growths than surgery with the cold knife.

## NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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**Acute Diseases of the Brain Due to Functional Disturbance of the Circulation.**—DE VRIES (*Arch. Neurol. and Psychiat.*, 1931, 25, 227) presents 4 cases in which the localized brain symptoms were due to elective softening of parts of the cortex and for which no organic vascular lesions could account. These cases are described in detail both clinically and pathologically. Case 1 was a toxemia of pregnancy, as evidenced by headache, premature delivery, icterus and convulsions. In addition, there was a mild chronic arteriosclerosis of the larger arteries at the base and of smaller intracortical arteries, together with chronic degeneration of ganglion cells. Foci of necrobiosis were found scattered indiscriminately in all of the layers of the cortex. These foci could not be explained by an organic change in the bloodvessels, and



it is not likely that a simple toxic action by the toxemia of pregnancy would cause such necrobiosis, because that theory would not explain the thromboses which were found in the foci nor the fatty degeneration of the vessel walls in other places. The author decides that: "One may, therefore, assume that the toxin acted on the arteries, causing a spasm which secondarily, through ischemia, caused macular necrosis of the nerve parenchyma and of the vessel walls themselves. The thrombosis probably occurred after the circulation had been restored; the hemorrhages in the necrotic parts occurred also after some circulation was present again." The patient in Case 2 had, in the fifth month of pregnancy, an attack of eclampsia or uremia. After Cesarean section the convulsive attacks stopped and the blood pressure came down to normal. Fever developed, however, and probably two days later paralyzes were noted. At autopsy no organic vessel lesion was found to explain the softened laminated cortical areas in the brain, although there were thromboses of various pial vessels in other places. Fresh changes, due to septicemia, were apparent in many places—they were of the usual character: thromboses or small necroses with hemorrhage. Although the lesions found were due to cortical ischemia, the author finds it quite difficult to ascertain the cause. He remarks that: "It may be that the reverting of the blood pressure from its initial high value to the normal level played a more important rôle than had hitherto been believed." In Case 3 there was a fulminating encephalitis after hard exercise and exposure to the sun. On the fifth day of the disease there was a gradually progressing hemiplegia. From the first day increased intraeranian pressure was present, and the coma had gradually increased. Cerebral edema or venous stasis, or both, might have been present, but these conditions do not cause necrosis of the gray matter unless aided by general anemia or vessel spasm. Here, as in Case 2, although there were areas of softening, which areas were laminated, there were found only normal vessel walls. The author here remarks that: "It is not now possible to give an explanation of the pathogenesis of the softening in this case. . . ." Case 4 had a severe gunshot wound, followed by severe shock. There was an infection of his wounds followed by septicemia, and death occurred 6 weeks later. Autopsy revealed hypertrophic meningitis, one encephalomalacic area in the left insula, and laminated softening of the gray matter around the parietal operculum and in the depth of the interparietal sulcus. In his comments on this case the author states that: ". . . no data are available to prove when the softening occurred, but probably this happened soon after the blood pressure fell to a very low level during the severe shock, which lasted for more than a day . . . sudden and prolonged intense fall of the blood pressure must have resulted in cerebral anemia with localized necrosis." The 4 cases described had two important points in common: (1) The softening was nearly exclusively localized in the gray matter, and in Cases 2, 3 and 4 took the form of laminated necrosis; (2) no organic change in the bloodvessels could be found to account for the necrosis.

**Cerebral Birth Conditions With Special Reference to Cerebral Diplegia.**—PATTEN (*Arch. Neurol. and Psychiat.*, 1931, 25, 453) reports 46 cases of cerebral birth pathology. These cases he has divided into

two groups: (a) The first comprising those in which labor was considered in every respect normal; (b) those in which there was a definite history of difficult labor. The author defines a normal labor as "one which was not prolonged, in which the presentation was usual and no anesthetics or instruments were used and in which birth was not precipitated and the delivery could, in all respects, be considered spontaneous." The term "difficult labor," he states, is the exact opposite and includes Cesarean section. A composite summary of the two groups is given. Of his cases, 19 fall into the difficult labor group and 17 into the normal group. The sexes are about equally divided. The children of the difficult labor group never sat alone in 26 per cent of the cases and in the normal group in 25 per cent; never walked alone in 31 per cent of the difficult labor group as compared to 40 per cent in the normal group; 21 per cent of the difficult labor group never talked as compared with 29 per cent of the normal labor group. Frank evidence of motor disability was not observed in the majority of instances in both groups until sometime after birth. The usual history given was that these children were not considered abnormal until the time came when ordinarily they should be carrying out some of the motor functions of their age period. Not infrequently they were brought with the complaint that they did not sit up, could not walk or had never talked. The most interesting feature of the group, taken as a whole, was evidence of involvement of the pyramidal tract in a group in which labor was considered normal. The incidence of unilateral spasticity was greater in the difficult labor group, 21 per cent as compared with 11.1 per cent in the normal group. The remaining cases also offered a striking contrast, for the difficult labor group had 35.8 per cent, with no evidence of involvement of the pyramidal tract as compared to 11.1 per cent in the normal labor group. The occurrence of abnormal movement was not as great as one would expect. Nearly one-half of the total number showed such movements as the choreiform, athetoid and definite incoordinations in both groups, 47 per cent in the difficult labor and 48 per cent in the normal group. Convulsions were not as frequent as one might have expected: they occurred in 30 per cent of the difficult labor group as compared with about 10 per cent in the normal labor group. The estimation of intelligence in many cases was difficult. In the normal group intelligence was considered defective in all but 1 case; that is, in 96 per cent there was an estimated intelligence deficit. On the other hand, the difficult labor group had 6 cases in which the children were considered normal and 13, or 68 per cent, defective. The author remarks that from these data he believes it is possible to state that, irrespective of birth history, certain syndromes appear, showing practically identical symptoms. That "there is a disturbance of motor function more or less symmetrically distributed, giving evidence of disease or defect of the motor equipment of the individual and an accompanying low level of intelligence." He concludes that: "The frequent occurrence of bilateral motor involvement, together with defect in intelligence, indicates something more than the effects of trauma or vascular accidents in the neurologic conditions of the newborn infant. There exists probably a developmental defect or arrest which concerns either the integrity of the cortical cells or the proper myelination of the corticospinal tracts and association fibers."

## PATHOLOGY AND BACTERIOLOGY

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The Distribution of Lipoid in a Case of Niemann-Pick's Disease Associated With Amaurotic Family Idiocy.—SOBOTKA, EPSTEIN and LICHTENSTEIN (*Arch. Path.*, 1930, 10, 677) reported a case of Niemann-Pick's disease occurring in a child, aged 10 months, who also presented evidences of amaurotic idiocy and who succumbed 8 months from the time that first symptoms were noted. Clinically the child presented enlargement of liver and of spleen, brownish pigmentation of skin and central red spots in the maculae of both eyes. The total blood fat was 1430 mg.; blood cholesterol, 290 mg.; serum calcium, 12.2 mg.; serum phosphorus, 3 mg. Blood smears showed vacuolation of lymphocytes. At autopsy the liver weighed 180 gm. and all internal lymph nodes were enlarged and yellow. Sections showed large round or polygonal cells with diffuse vacuolization of their cytoplasm, throughout spleen, liver, lymph nodes, bone marrow, lung, kidney and intestine. These cells contained no neutral fat, contained some doubly refractive lipoids (cholesterol?) and large amounts of other lipoids. Sections of brain showed changes typical of those observed in amaurotic idiocy. The lipid analyses showed an increase in lipid phosphorus, in cholesterol to a lesser degree, and a depletion and disappearance of neutral fat from the organs of the body. This latter is a specific finding of Niemann-Pick's disease. The absence of kerafin serves to differentiate the condition from Gaucher's disease. This case tends to support the idea that Niemann-Pick's disease represents a widespread lipid degeneration and that amaurotic idiocy represents the same degeneration limited to the central nervous system.

The Occurrence and Nature of Spontaneous Arteriosclerosis and Nephritis in the Rabbit.—NUSUM, ELLIOT, EVANS and PRIEST (*Arch. Path.*, 1930, 10, 697) point out that in rabbits two types of so-called "spontaneous" arteriosclerosis occur. These are: (1) An elevated intimal lesion, and (2) medial degeneration, with calcification, and depression of the overlying intima. These two types of lesions occurred among 190 normal animals in the incidence of 3.1 per cent and 5.3 per cent respectively. In the same group of animals "spontaneous" nephritis occurred in 2.1 per cent. The nephritis was either focal in character, giving no clinical evidence of its presence, or was of a diffuse type giving rise to albuminuria and blood chemistry changes. In a group of 20 animals chosen because of evidence of spontaneous nephritis 10 were fed on a liver diet for 1 year. These animals showed somewhat

more extensive arterial lesions than noted in the animals fed upon a more representative diet. The liver diet appeared, also, to increase the degree of the renal damage, as evidenced clinically and pathologically. In regard to the etiology of these conditions, the high protein diet and infection are considered as possible factors.

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**The Transmissibility of Tick-bite Fever Virus to Guinea Pigs.**—PIJPER and DAU (*Brit. J. Exp. Path.*, 1930, 11, 287) have shown that the intraperitoneal injection of from 1 to 2 cc. of blood from patients suffering from tick-bite fever produced fever in guinea pigs. The normal rectal temperature of these animals was determined by them to be never greater than 102°. After the injection of blood the temperature rose 1° or 2° for several days. The temperature then dropped to normal, but was followed by a second rise which was more pronounced than the first one. Fever of similar nature was produced in a second group of animals by intraperitoneal injection of blood or brain pulp from the originally injected animals. In one instance the fifth animal passage was reached. Passages seemed to increase the virulence as judged by the temperature chart. Postmortem examination of these animals showed enlarged spleens, enlarged adrenals and markedly injected meninges. The authors concluded that South African tick-bite fever is caused by a living virus of the Rickettsia class.

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**Iron Storage in Splenectomized Rabbits.**—FOWWEATHER and POLSON (*Brit. J. Exp. Path.*, 1930, 11, 362) studied the storage of iron in the organs of rabbits to which colloidal iron was administered intravenously. One group of animals was splenectomized while the others were left intact. In these two groups each animal received 160 mg. of iron. A third group was kept as a control. Animals were killed in pairs at various time intervals up to 2 months and the lungs, livers, spleens and kidneys subjected to chemical and histologic examination. The outstanding feature of the results was the close similarity between the figures obtained for the first two groups of animals. The absence of the spleen did not materially affect the distribution of iron in the organs. The liver was the principal site of iron storage insofar as actual amounts were concerned. The concentration of iron in the spleen was much greater than in the liver, but the total amount stored there was minute in comparison. Histologic examination confirmed the results of chemical analysis. Pulmonary embolism of slight degree was constantly found, but active phagocytosis of iron thus held in the lung was in progress. The results did not yield any definite information on the transference of iron from the lungs to the liver. However, a transportation of iron from the lungs was suggested by the fact that in both series the lung iron content decreased steadily with passage of time.

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**Sclerosis of the Pulmonary Artery and Arterioles.**—ROSENTHAL (*Arch. Path.*, 1930, 10, 717) reports 3 cases of primary arteriosclerosis of the pulmonary artery, all of whom presented cough, dyspnea, cyanosis, edema and hypertrophy of the right ventricle of heart, thus being comparable to the syndrome described by Ayerza. The ages of the

patients varied from 43 to 48 years. On postmortem examination the lungs were dark gray, subcrepitant and moderately collapsed. Microscopically there was no peribronchial fibrosis or inflammatory reaction. The alveolar walls presented capillaries, some of which were dilated, some contracted, while many showed endothelial necroses. The main trunk of the pulmonary artery was slightly dilated. From the second order of vessels downward atheromatous changes became more marked. The earliest changes were a thickening of the media, due to muscle hypertrophy and elastic-tissue increase, and splitting of the internal elastic laminae. Occasionally early hyalin and fatty changes in media and in intima accompanied the early thickening. As the regressive changes advanced the intima became thicker, fibrous-tissue proliferation occurred and the media, because of similar advancing changes, became thinned out. Thrombi became numerous. This process advanced to the point where the lumina of the vessels were obliterated either by organizing thrombus or by intimal proliferation. All 3 patients were in their occupations exposed to aspiration of gases or of particulate matter. These the author believes lead to chemical or mechanical irritation of the capillaries, with resultant spasm and even endothelial necrosis. This calls forth greater activity of the smaller arteries, with resultant muscle hypertrophy and elastic-tissue increase. With continued demands degenerative changes are established which give rise to the peculiar sequence of events described.

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## HYGIENE AND PUBLIC HEALTH

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**The Types of Tubercle Bacilli Found in Tuberculous Lesions and in Nontuberculous Tissue in Man.**—ARONSON and WHITNEY (*J. Infect. Dis.*, 1930, 47, 30) states that tubercle bacilli obtained from latent and progressive lesions and from nontuberculous tissue fall into two distinct groups with occasional atypical strains. The human type of tubercle bacillus is characterized by luxuriant growth on glycerol agar and slight pathogenicity for the rabbit. The bovine type of tubercle bacillus is characterized by sparse growth in early generations on glycerol agar and high pathogenicity for the rabbit. The atypical strains may grow luxuriantly on glycerol agar and be highly pathogenic for the rabbit, or the cultures may grow sparsely and be slightly pathogenic for the rabbit. The glycerol reaction curve was not found to be specific for the respective types. No difference between the types

could be detected by means of the complement fixation reaction. From latent tuberculous lesions of human autopsy material there were isolated 83 cultures of the human type of tubercle bacillus, 3 cultures of the bovine type and 2 atypical strains. From progressive tuberculous lesions 96 cultures of the human type and 3 cultures of the bovine type were isolated. From lung tissue, pulmonary lymph nodes and mesenteric lymph nodes free from tuberculous lesions there were isolated 38 cultures of the human type and 2 atypical cultures. Three of the bovine cultures were obtained from guinea pigs inoculated with latent pulmonary tuberculous lesions from patients, aged 42, 65 and 65 years. Three cultures of bovine tubercle bacilli were obtained from the mesenteric nodes of children, aged 10 and 12 months, and from the lung of the second child. The atypical strains of tubercle bacilli were isolated from 2 patients, aged 57 and 70 years. Two of these cultures were obtained from nontuberculous lesions and 2 from a latent tuberculous lesion.

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**Recent Progress in Studies of Undulant Fever.**—HASSELTINE (*Public Health Reports*, 1930, 45, 1660) studied the prevalence of undulant fever based on 442 cases which could be divided into three groups: (a) Those without significant exposure to livestock or carcasses (mostly urban cases); (b) rural cases having direct contact with livestock; (c) urban cases having direct contact with livestock or carcasses. These may be referred to as the milk, farm and meat groups. Group I, the milk group, had 198 cases (103 males, 95 females). Group II, the farm group, had 200 cases (191 males, 9 females). Group III, the meat group, had 44 cases (43 males, 1 female). The age distribution shows few cases below 10 years, and 67 per cent of cases occurred between 20 and 50 years of age. Every state in the Union furnished 1 or more cases. Bang's bacillus, the cause of contagious abortion in cattle, is considered the essential cause of undulant fever, as it prevails in the United States. Either of the varieties found in this country may infect man. Cattle may become infected with either goat or hog strains. Pasteurization of milk is regarded very effective in preventing the disease. This is borne out by the absence of the disease in cities having adequate pasteurization. Aside from cases due to milk, there is a large group of cases due to contact with infected animals or animal products, but there is no satisfactory means of dealing with this group of cases at the present time. Serologic tests in man and animals are regarded as aids in reaching diagnoses.

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**The Relation of Temperature and Humidity to the Course of a Bacillus Enteritidis Infection in White Mice.**—Recent studies on the epidemiology of typhoid fever in Palestine have led to the conclusion that the seasonal epidemicity of intestinal infections could only be accounted for by the assumption that there is a seasonal variation in the resistance of the host to this type of infection. It was assumed that climatic factors, such as temperature, humidity, radiation, singly or in combination, effect disturbances in the physiologic equilibrium of the host which render him more or less susceptible to the invasion and localization of this group of microbes. In order to test this hypothesis

KLIGLER and OLITZKI (*Am. J. Hyg.*, 1931, 13, 349) undertook a series of experiments on the effect of certain environmental factors on the course of an enteric infection. White mice from the same stock and of the same age infected with the same number of *Bacillus enteritidis* and kept at different temperatures and humidities reacted differently to the infecting microbes. At a low temperature and a high relative humidity (10° to 12° C. and 90) the infection is more severe than at higher temperatures (20° and 30° C.) and the same humidity. The fatality rate is the same but the incidence of liver abscesses is higher. At 30° C. the mice kept at a relative humidity of 90 are more severely affected than those kept at a relative humidity of 35°. Under the latter conditions the development of the infection is more rapid, but it is mild or inapparent in character, clears up rapidly and leads to relatively few deaths in comparison with the group kept at a high relative humidity. At 20° C. a higher humidity seems more favorable than a lower one; but the differences are not marked. It appears that the critical factor is not temperature alone nor humidity alone, but the combination of the two; probably the so-called "effective temperature." The authors state that these results are only suggestive and that much more work is required to clear up this problem. They are, however, significant and support the assumption of a seasonal variation in host resistance due to environmental influences. The method employed opens the possibility of a systematic study of the problem, and the investigations are being continued.

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**Heliotherapy and the Peripheral Blood.**—HOEFFEL and LYONS (*Am. J. Dis. Child.*, 1930, 40, 484) state that there is no justification for the belief that light rays, considered either collectively as including the entire spectrum or individually as ultraviolet rays, have any specific effect on the blood. The effect of light on the healing of a pathologic process, such as tuberculosis, cannot be distinguished from that exerted by other factors, the beneficial influences of which are well recognized.

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# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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## ORIGINAL ARTICLES.

### DIABETES MELLITUS AND ITS COMPLICATIONS.

#### AN ANALYSIS OF 827 CASES.

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THERE are few diseases more commonly attended by complications than diabetes mellitus. The nature of this disturbance is such that the patient is predisposed not only to a variety of infections but to arteriosclerosis as well. An analysis of a large group of unselected cases of diabetes reveals in an impressive manner how serious are the complications of diabetes. The object of this study is to determine what diseases most commonly are associated with diabetes, and in what manner this association affects diabetics. For this purpose the records of 827 diabetics treated at the Milwaukee County Hospital from January 1, 1922, to January 1, 1930, were analyzed. This series is not made up of cases selected for hospital care on the basis of complications. The cases in this report represent a fair cross-section of all indigent diabetics in the community.

TABLE 1.—CASES OF DIABETES MELLITUS AT MILWAUKEE COUNTY HOSPITAL FROM 1922 TO 1930 (827 CASES).

	No. of cases.	Per cent total cases.	Improved.		Unimproved.		Died.	
			No.	Per cent.	No.	Per cent.	No.	Per cent.
Total cases . . . . .	827							
Without complications . .	146	17.63	142	97.26	3	2.05	1	0.69
With complications . . .	681	82.37	428	64.22	14	2.05	239	35.18



TABLE 2.—SUMMARY OF THE VARIOUS COMPLICATIONS OF DIABETES MELLITUS IN THIS SERIES WITH AGE AND SEX INCIDENCE.

	No. of cases.	Per cent diabetic cases (No. 827).	Improved.		Unimproved.		Died.		Average age of males.	No. of males.	Average age of females.	No. of females.
			No.	Per cent.	No.	Per cent.	No.	Per cent.				
1. a. Primary coma . . . . .	20	2.41	18	90.0	0	0	2	10.0	47	13	24	7
h. Secondary coma . . . . .	13	1.57	3	23.0	0	0	10	76.9	47	7	32	6
Total coma (a + b) . . . . .	33	3.99	21	63.6	0	0	12	36.3	47	20	28	13
2. Cardiorenal vascular disease, total . . . . .	273	33.01	136	49.8	7	2.5	130	47.6	57	144	57	129
Cardiac . . . . .	40	4.83	17	42.5	1	2.5	22	55.0	54	19	50	21
Nephritis . . . . .	12	1.45	8	66.6	0	0	4	33.3	53	8	55	4
Apoplexy . . . . .	25	3.02	8	32.0	0	0	17	68.0	61	10	59	15
Arteriosclerosis . . . . .	124	15.00	68	54.8	4	3.2	52	41.9	60	69	55	61
Gangrene . . . . .	72	8.70	35	48.6	2	2.7	35	48.6	57	38	62	34
3. Infections, total . . . . .	86	10.39	53	67.4	0	0	28	32.5	50	42	44	44
Pneumonia . . . . .	16	1.93	2	12.5	0	0	14	87.5	59	6	37	10
Influenza . . . . .	1	0.12	1	100.0	0	0	0	0	62	1	0	0
Upper respiratory tract . . . . .	13	1.57	11	84.6	0	0	2	15.3	40	7	57	6
Otitis media, mastoiditis . . . . .	5	0.60	4	80.0	0	0	1	20.0	32	1	4	35
Gall bladder disease . . . . .	5	0.60	5	100.0	0	0	0	0	0	0	50	5
Erysipelas . . . . .	7	0.84	6	85.7	0	0	1	14.2	69	2	60	5
Abscess of skin . . . . .	6	0.72	4	66.6	0	0	2	33.3	56	4	61	2
Abscess of other organs . . . . .	12	1.45	9	75.0	0	0	3	25.0	50	10	55	2
Septicemia . . . . .	3	0.36	0	0	0	0	3	100.0	59	1	48	2
Mononucleosis, infectious . . . . .	1	0.12	1	100.0	0	0	0	0	0	0	11	1
Hepatitis, infectious . . . . .	1	0.12	1	100.0	0	0	0	0	27	1	0	0
Glossitis . . . . .	1	0.12	1	100.0	0	0	0	0	52	1	0	0
Infect. and inflam. genitourin. system . . . . .	15	1.81	13	86.6	0	0	2	13.3	44	8	53	7
4. Tuberculosis, pulmonary . . . . .	40	4.83	22	55.0	2	5.0	16	40.0	41	28	43	12

5. Carcinoma	8	0.96	2	25.0	2	25.0	4	50.0	59	4	51	4
6. Syphilis	31	3.74	22	70.9	0	0	9	29.0	54	19	49	12
7. Miscellaneous complications, total	210	25.39	169	80.4	3	1.4	38	18.0	47.5	124	54	86
Alcoholism	3	0.36	1	33.3	0	0	2	66.6	49	2	43	1
Anemia, pernicious	3	0.36	3	100.0	0	0	0	0	71	3	0	0
Asthma, bronchial	1	0.12	1	100.0	0	0	0	0	0	0	43	1
Caries, dental	58	7.01	50	86.2	0	0	8	13.7	55	45	61	13
Cirrhosis, hepatic	3	0.36	1	33.3	0	0	2	66.6	38	1	68	2
Dermatitis	7	0.84	6	85.7	0	0	1	14.2	55	5	41	2
Embolism, pulmonary	1	0.12	1	100.0	0	0	0	0	22	1	0	0
Emphysema, pulmonary	5	0.60	4	40.0	0	0	1	20.0	59	4	73	1
Epilepsy	3	0.36	3	100.0	0	0	0	0	42	3	0	0
Fractures	12	1.45	10	83.3	1	8.3	1	8.3	61	6	57	6
Hernia	8	0.96	7	87.5	0	0	1	12.5	58	7	56	1
Hypertension, essential	28	3.38	21	75.0	0	0	7	25.0	47	8	57	20
Hyperthyroidism	8	0.96	5	62.5	1	12.5	2	25.0	36	2	40	6
Morphinism	1	0.12	1	100.0	0	0	0	0	31	1	0	0
Neuritis	5	0.60	4	80.0	0	0	1	20.0	56	4	55	1
Neurasthenia	1	0.12	1	100.0	0	0	0	0	46	1	0	0
Optic complications	19	2.29	15	78.9	0	0	4	21.0	52	10	59	9
Osteoarthritis	4	0.48	4	100.0	0	0	0	0	64	3	77	1
Osteomyelitis	1	0.12	1	100.0	0	0	0	0	0	0	62	1
Pleurisy	2	0.24	1	50.0	0	0	1	50.0	18	1	58	1
Pregnancy	3	0.36	3	100.0	0	0	0	0	0	0	26	3
Psychosis	18	2.17	12	66.6	1	5.5	5	27.7	55	7	63	11
Scurvy	1	0.12	1	100.0	0	0	0	0	53	1	0	0
Singultus	1	0.12	1	100.0	0	0	0	0	45	1	0	0
Suicide	1	0.12	0	0	0	0	1	100.0	48	1	0	0
Surgical cases	4	0.48	4	100.0	0	0	0	0	25	2	39	2
Ulcer, peptic	1	0.12	0	0	0	0	1	100.0	41	1	0	0
Varices, hemorrhoids	8	0.96	8	100.0	0	0	0	0	49	4	54	4

**Analysis of the Cases.** Of the 827 cases of diabetes studied there were 146 (17.63 per cent) with no complication. As shown in Table 1, of the 146 uncomplicated cases 142 (97.26 per cent) improved and 3 (2.05 per cent) of them were unimproved. In 681 cases (82.37 per cent) there were one or more associated diseases. Of the 681 complicated cases 428 (69.2 per cent) died. The total number of complicating diseases was 75 and they are tabulated under 52 separate headings in Table 2. Table 2 indicates the various complications and shows the status of the patient after treatment. For the purpose of clearness the 75 types of complications are grouped under seven main heads, as follows: (a) Diabetic coma; (b) cardiorenal vascular diseases; (c) infections; (d) tuberculosis; (e) carcinoma; (f) syphilis; (g) miscellaneous.

The age and sex incidence of the group without complications is shown in Table 3, and that of the group with complications is furnished in Table 2. The number of males and females throughout the series was fairly equal except in the miscellaneous group which comprises 124 males and 86 females. In the entire series 453 were males and 374 females. The general average age of patients was computed for each type of complication. It is shown that the general average age ranged from 11 to 71 years, and that by far the most of the patients were over 45 years. Although the age incidence for this series of cases is high, nevertheless it conforms with the average age of the general population of the institution.

TABLE 3.—AGE AND SEX INCIDENCE OF DIABETIC PATIENTS WITHOUT COMPLICATIONS.

	No. of cases.	Average age of males.	No. of males.	Average age of females.	No. of females.	General average ages.	Youngest.	Oldest.
Total cases . . .	146	40.8	72	47.1	74	43.9	7	78
Improved . . .	142	40.8	71	46.7	71	43.8	7	78
Unimproved . . .	3	0	0	55.3	3	55.3	50	63
Died . . .	1	35.0	1	0	0	35.0	35	35

**Diabetic Coma.** Coma formerly was the outstanding complication of diabetes, but with modern treatment it can be controlled. Always there will be some deaths from coma, either because treatment is begun too late or because other complications develop which render the treatment for coma ineffective. In this analysis we have separated primary coma from secondary coma. It is obvious that the results of treatment will be much better in the primary than in the secondary group. As shown in Table 2, there were in all 33 cases of diabetic coma; of these 20 were of the primary and 13 were of the secondary variety. In the primary group 2 died and 18 recovered, while in the secondary group 10 died and 3 recovered.

ered. A striking feature noted is that for primary coma the average age of males was 47, while the average age for females was 24 years. No female died in primary coma, and the ages of the 2 men dying in coma were 49 and 58 years respectively. None of our younger patients died in primary coma and all of them responded satisfactorily to treatment. In secondary coma the presence of overwhelming infections or of some other serious complications raised the mortality rate. The mortality figures of coma for the period of 1922 to 1926 were decidedly higher than those for the period of 1926 to 1930. A better understanding of the action of infection and fever upon insulin, an appreciation of the value of larger quantities of insulin and fluid in the treatment of coma and, finally, added clinical experience are among the chief reasons for a lower death rate during the past four years.

**Cardiorenal Vascular Diseases.** An inspection of Table 2 reveals that the cardiorenal vascular group with 273 cases constitutes the most common complication in this series. Gangrene occurred in 72 patients (8.7 per cent). Of these 35 (48.6 per cent) died. The total number of cases of gangrene occurring in the hospital population for the same period of time was 175. Of these 75 (42.8 per cent) died, showing a mortality rate that almost paralleled that of the diabetic group. The diseases of the heart and kidneys were for the most part produced by arteriosclerosis. There were 40 diabetics (4.8 per cent) with heart disease. Heart failure with death occurred in 22 (55 per cent) of them. During the period of time covered in this report there were 2871 cases of cardiac disease (5.7 per cent of the population of the hospital); 1069 (36.5 per cent) of them died. On comparing the percentage of patients suffering from cardiorenal vascular disorders in a public general hospital with that of diabetics who are affected in the same manner it would appear that there is little direct relationship between the two groups. However, the group of patients with diabetes and cardiac diseases showed a higher mortality rate by 18 per cent than the nondiabetic group. Undoubtedly, there is now a higher incidence of diabetes among patients with vascular diseases than was found before 1922. This fact may be explained on the assumption that the present-day diabetic more frequently lives on into the arteriosclerotic period of life by virtue of insulin than did the diabetic prior to the discovery of insulin.

**Infections.** A variety of infections other than gangrene were found in 86 cases, giving the group an incidence of 10.3 per cent. Any infection is borne badly by the diabetic, but pneumonia is an especially disastrous complication. There were 1200 patients with pneumonia admitted to the hospital during the period of this study and 654 (54.5 per cent) of them died. At the same time there were 16 diabetics with pneumonia and 14 (87.5 per cent) died. In 3 cases it was difficult to determine whether or not pneumonia was

present because acidosis was so severe. The changes in breathing and in the leukocyte counts were of the type easily confounded with those of advanced primary coma. Autopsy, however, was done in 2 of the 3 cases and the diagnosis of pneumonia was substantiated. Rheumatic fever is known to be a rare complication of diabetes. In this series no case of rheumatic fever was found. The occurrence of peptic ulcer in only 1 patient among our diabetics came as a distinct surprise, since there was an incidence of 167 cases of peptic ulcer in the hospital during the same period. One other patient had gastric hemorrhage and melena in the course of coma and a diagnosis of ulcer was made. At autopsy no ulcer was found.

**Tuberculosis.** Among our diabetics there were 40 cases of pulmonary tuberculosis or an incidence of 4.83 per cent. Sixteen of them died, giving a mortality rate of 40 per cent. Of the 40 diabetics who had tuberculosis 14 were considered to be free from tuberculosis when diabetes was first discovered, while 26 had both diabetes and tuberculosis when diabetes was diagnosed. Coincidentally there were 1630 cases (3.26 per cent) of pulmonary tuberculosis among the hospital population, and of these 398 (24.4 per cent) died. Although the incidence of pulmonary tuberculosis is not much higher among the diabetic than among nondiabetic, yet the death rate is considerably greater in the diabetic group.

**Carcinoma.** Malignant disease occurred 8 times in our series, and it is noted that 4 of the patients died in the hospital. Carcinoma of the body and tail of the pancreas was found in 1 case. In other cases it appeared that diabetes had no relationship to the malignancy. Considering the frequency with which cancer appeared in the records of the hospital, we expected to find a higher rate of incidence of cancer among our diabetics. Eight hundred and sixty-two cases (1.7 per cent) admitted to the hospital during the period of this study had carcinoma. The mortality rate during their stay in the hospital for the total cases of carcinoma was 53.1 per cent and for the diabetic group it was 50 per cent.

**Syphilis.** Syphilis and diabetes were found together in 31 patients (3.74 per cent). Eight of the patients died, giving a mortality rate of 29 per cent for the group. The total number of syphilitics admitted to the hospital for this period was 1647 (3.3 per cent of all admissions). Of the total number of syphilitics admitted to the hospital 296 (18.1 per cent) died. Antisyphilitic treatment was followed by apparent recovery from diabetes in 2 syphilitic diabetics. In the other diabetics with syphilis antisyphilitic treatment appeared to have no effect on the diabetes other than that expected from any syphilitic under specific treatment.

**Miscellaneous.** Miscellaneous complications totalled 210 (25.39 per cent). Individually this group is not very impressive; but when considered collectively they constitute a serious problem in the successful management of the diabetics. The occurrence of hyper-

thyroidism only in 8 cases (0.96 per cent) was unexpected. It was thought that this complication would be more frequent in this district. There were 618 cases of hyperthyroidism (1.24 per cent of the entire hospital population treated in the hospital during this period of observation). For example, a study of 38 cases of diabetes combined with states of hyperthyroidism was reported by Wilder.<sup>1</sup> He found the association of diabetes and hyperthyroidism occurred with a frequency of about 1.1 per cent of all cases of hyperthyroidism. These figures, however, are not at variance with those cited by others who have reported upon the incidence of goiter and diabetes in the Middle West.

**Discussion.** It is obvious that a diagnosis of diabetes alone is often incomplete. When the diabetic's progress is unsatisfactory after he has been rendered sugar-free, a complication should be seriously considered. Many complications are easily detected, such as gangrene, apoplexy or carbuncles; but there are others, for example, early tuberculosis, carcinoma and coronary disease of the heart which often are hidden and which at times require careful examination to diagnose them. Uncomplicated diabetes usually is a benign disease that responds readily to routine treatment; but when a complication, especially one of an infectious nature, attacks the diabetic a comparatively benign disease becomes converted into a grave one. The prevention of complications should be the aim in the management of diabetics. Coma is largely preventable. Gangrene and infections often may be prevented.

The disparity between our mortality rate in coma and that of others who have reported on the subject may be explained partly by the advanced years of many of our patients. Our patients were, on the average, older than those seen in private practice. Furthermore, coma was usually far advanced before the patient was brought into the hospital. This is well illustrated in our 2 patients who died of primary coma; both had been in coma for more than 36 hours before entering the hospital.

When a discussion of one's mortality rate in coma arises a brief statement seems warranted regarding the method of management. In all of the cases of coma reported here insulin was used. The application of heat, the use of stimulants, eliminants and other adjuncts to treatment will not be discussed. During the earlier years of treatment with insulin the doses of insulin used were too small. Fear of insulin shock chiefly prevented the use of larger doses. Glucose solution and other fluids were not used in sufficient quantities to produce beneficial results. The successful treatment of coma depends upon the use of an adequate amount of insulin and a sufficient quantity of fluids to overcome acidosis and dehydration. For the past 4 years insulin in doses of 40 to 50 units had been given every 2 hours until the urine became sugar-free and the blood sugar was reduced to almost a normal level. Fluids are sup-

plied in large quantities. If the patient is in a precoma state diluted orange juice, tea, coffee or water are given by mouth in small quantities every half hour. It is unwise to give more than 100 cc. of fluid by mouth every half hour, because acute dilatation of the stomach may follow the administration of a large amount of fluid. When little or no fluids can be taken by mouth solutions of glucose and saline are given intravenously and subcutaneously, and plain water is given by rectum. One thousand cubic centimeters of 10 per cent glucose are administered intravenously, 1000 cc. of 1 per cent saline subcutaneously and 1000 cc. of water per rectum are given during the first 12 hours of treatment. It is our custom to add 1 unit of insulin for every 2 gm. of glucose directly to the intravenous solution. The solution is well agitated before it is given. This quantity of fluid usually is adequate to overcome the profound oliguria or anuria which are found in severe cases. An exception to this plan is made when a patient arrives in advanced coma. For this condition as high as 75 units are given intravenously at once, followed by 40 units every hour until the blood sugar begins to fall and the sugar in the urine becomes diminished. The periods then between doses of insulin are increased and the quantity decreased until the blood sugar is normal. Although no patient was seen who suffered any permanent ill effects from an overdose of insulin, nevertheless the reckless use of large quantities of insulin is to be condemned.

Alkalies were not given in any form to patients with acidosis. During the past 5 years we have given considerable attention to the kidney and the urinary excretion in diabetic coma. When anuria or profound oliguria develops in the presence of coma the prognosis is bad. The use of large quantities of fluid intravenously and by other routes frequently is followed by diuresis. The deciding factor in the success or failure of treatment often depends on this diuresis. Undoubtedly the relief of dehydration by administration of large quantities of fluids has not had sufficient attention in general. Lawrence<sup>2</sup> reported upon the beneficial effects of extremely large quantities of fluids in treating 2 desperate cases of coma. He used in 1 case 5300 cc. of fluids, and of that amount 4000 cc. were given intravenously during a period of 10 hours. Coburn<sup>3</sup> has recently emphasized the importance of diuresis in diabetic coma and states that in 18 per cent of his patients coma followed a renal shutdown. Warren,<sup>4</sup> pointed out that in coma the chief burden of eliminating acetone bodies is thrown on the kidneys, and that these substances profoundly injure the epithelium of the renal tubules.

Renal arteriosclerosis in a diabetic past 40 years is commonly found, and is frequently associated with a high renal threshold for sugar. Providing that renal insufficiency has not developed, large quantities of acetone and diacetic acid may be excreted with the urine. From clinical experience with coma one is led to believe

that when the injurious effect of acidosis is added to a kidney already damaged by arteriosclerosis the outcome of the disease often is fatal.

The disorders of the cardiorenal vascular type are among the commonest complications of diabetes. The reason for the high incidence of these complications is that both diabetes and the degenerative diseases of the cardiorenal-vascular system show a sharp rise between the ages of 40 to 55 years. The relationship between arteriosclerosis and myocardial disease is better understood now than ever before, but a breakdown of the cardiovascular system of the diabetic is often almost complete before it receives adequate attention. Since diabetes of older people is usually mild in type, complications such as the cardiovascular variety should especially be guarded against. Circulatory disturbances of the feet produced by arteriosclerosis are among the severest complications a diabetic may develop. Prevention of gangrene of the legs is one of the important functions of the attending physician. For prevention of gangrene Joslin<sup>5</sup> has stressed the importance of keeping the feet clean and avoiding even minor injuries to the feet. Despite careful treatment arteriosclerotic gangrene may develop.

The diabetic is more sensitive to the action of infection than is a normal person. Infections not only tend to develop more rapidly in the diabetic but they aggravate the diabetes itself. Whether infection makes diabetes worse by its action on metabolism in general, or by directly attacking the islands of Langerhans, has not been definitely decided. Infections favor the onset of acidosis and coma. However, infections are less feared today than formerly for the reason that with insulin acidosis and coma may be controlled. Larger doses of insulin are required to control hyperglycemia in the presence of fever and infections than are necessary in the afebrile patient. Pulmonary tuberculosis is found among diabetics less often today than formerly. Nevertheless, it is an important complication in our series. Sevringhaus,<sup>6</sup> of Madison, Wis., states that tuberculosis was found rarely in his series of 500 cases. The difference between his figures and ours is interesting because his patients come from the rural communities of Wisconsin while ours come exclusively from the industrial district of Milwaukee. Fitz<sup>7</sup> recently reported that he found 35 cases of tuberculosis among 1529 diabetics (2.3 per cent). He quotes Wilder and Adams, of The Mayo Clinic, who saw 10 cases of tuberculosis among 1000 diabetics (an incidence of 1 per cent). Of greatest importance is the fact that tuberculosis must always be thought of and sought for among diabetic patients. Its early diagnosis is necessary if a successful result is to be obtained. Of 150 diabetic deaths reported by Lyon<sup>8</sup> 11 (7.3 per cent) were caused by tuberculosis. Among Joslin's<sup>5</sup> first 3000 diabetics there were 84 true diabetic patients with tuberculosis and among the remaining 3000 there were 43 cases.



In his series the number of fatal cases of diabetes with tuberculosis was 103 (81.1 per cent of the total cases, 127). As to prognosis, it is generally conceded that the tuberculous diabetic does badly. Curschmann<sup>9</sup> is of the opinion that the tuberculous diabetic has about as good a chance for recovery as the nondiabetic. This opinion is not in accord with our own experience.

Most of the published reports classify syphilis as a rare complication of diabetes, yet our study showed a high incidence of syphilis. Joslin<sup>10</sup> states that there was a history of syphilis or signs of syphilis in 55 (1.7 per cent) of his 3200 diabetics, while Lemann<sup>11</sup> showed that 3.6 per cent of his cases had syphilis. He (Lemann) believes there is evidence to show that diabetes is in some cases produced by syphilitic disease of the pancreas. The incidence of latent syphilis and diabetes has been investigated by Warthin and Wilson.<sup>12</sup> Diabetes, they believed, was frequently produced by syphilis. They had postmortem evidences of syphilis in every one of 6 autopsies done in diabetics. Labbé<sup>13</sup> claims that the syphilitic diabetic is rare. The coincidence of syphilis with diabetes he found was no more frequent than syphilis with other diseases. The opinion among most writers appears to be that syphilis is a rare contributory cause of diabetes. Striking improvement in several syphilitic diabetics has been seen in our clinic after antisyphilitic treatment.

The high mortality figures cited in this series of cases require brief comment. A comparison of the death rate in this series was made with the death rate in an equal number of diabetic patients treated in private practice by one of us. It was estimated that the mortality rate in the series treated privately was 21.5 per cent, in contrast to a 35.7 per cent mortality reported here. Patients entering a county hospital belong to a class of people who, as a rule, neglect themselves. Many of them have no home and no money, and consequently they have irregular meals and sleep. Usually they enter the hospital in an advanced state of impoverishment. They frequently regard a painless disease like diabetes with indifference and, therefore, allow themselves to become undernourished. Complications become well established before the patient consults a doctor. Frequently these patients refuse hospital treatment until they are in the last stages of the disease. The result then is that diabetes itself, as well as the complication, is well advanced when the patient enters the hospital. Delay in beginning treatment has been one of the outstanding causes of death among these patients. One other factor which tended to raise our mortality rate was the advanced age of many patients. Older patients do not tolerate complications well. Coma in a young patient is comparatively easy to manage, but when coma develops in an old arteriosclerotic person with an infection it is more difficult to obtain satisfactory results from treatment.

**Summary.** 1. An analysis has been given of the complications present in 827 cases of diabetes mellitus. The 75 various types of complications are listed and discussed under seven main headings.

2. Of the 827 cases 681 (82.37 per cent) were complicated by one or more diseases. This shows that a diagnosis of diabetes mellitus alone is often incomplete.

3. A complication usually interferes with the welfare of a diabetic and often causes a disastrous outcome. For this reason the early recognition and treatment, as well as prevention, of complications are among the chief aims in the management of diabetes.

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### A STUDY OF FIVE HUNDRED DIABETICS.\*

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IN the eight years since insulin has been available for our use 500 diabetic patients have been admitted to the Wisconsin General Hospital. These patients have been treated according to an essentially uniform plan. With a few exceptions, all have been under the care of the author during their hospital residence. With the assistance of Dr. W. S. Middleton a fundamental plan of therapy was developed during the first months of the insulin era. This has remained essentially unchanged throughout the series. This uni-

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formity of background should make some of the following data more significant.

**Plan of Treatment.** The diet plan of the hospital<sup>1</sup> involves the use of the Woodyatt type of ratios. The total fat is not allowed to vary significantly from the sum of twice the carbohydrate plus half the protein fed. Protein minimum is kept at 50 gm., except for infants. The calorie value of the diet is set at the minimum level which by trial will maintain approximately "normal" body weight. In obese cases alterations are made simply by reducing the fat content of such a prescribed diet to levels of 30 to 50 gm. daily. When the desired body weight has been reached the full fat quota is allowed again.

Admittedly there are many individuals who can economically use a higher fat ration, or proportionately less carbohydrate. It is dangerous to plan a routine type of therapy to include such unduly high fat diets. This is due not to the danger of ketosis or of fat intolerance but to the frequent objection of the patient to such a diet for continued use. The objection stated is general and will have specific exceptions. When our patients object to the carbohydrate limitation which we teach it is our practice to point out that the Woodyatt type of diet is economical in terms of insulin required, endogenous or injected. We frequently tell patients that they may have diets planned with larger amounts of carbohydrate and proportionately less fat. They understand that they will probably need more insulin on such diets. It is a very exceptional patient who elects to have more carbohydrate in the diet under these conditions.

It is impossible for us to tell how thoroughly and how persistently our patients follow their diets at home. Most of them return promptly to family physicians who have originally referred them to the hospital. Those who return for further care or who reply to letters of inquiry seem either to follow the diets faithfully or to be unwilling to submit to any restrictive routine at all.

We do not attempt to stop glycosuria by using undernutrition régimes followed by slow additions of food up to the requirement defined above. It appears economical of time to arrive as soon as possible at a maintenance diet, and to give insulin if necessary to stop loss of sugar. In many cases in which insulin is given at first it may be dispensed with before the discharge of the patient. There are other advantages to using insulin even though it may be dispensed with. In this way patients may learn under adequate supervision how to make the injections properly.

It is the aim to send patients home free from glycosuria. In young patients this is held to be inadequate as a goal, and the additional attempt is made to have the blood sugar before breakfast as near the normal level as is safe. The maximum insulin dosage allowed is insufficient to cause frequent reactions. Obviously there

are a few cases of very severe diabetes in young patients in whom not all these goals can be secured. In such a dilemma maintenance of weight, freedom from ketosis and avoidance of insulin reactions are the goals.

In no case is there any attempt to limit occupation or work. All patients are encouraged to get regular exercise and to make the amount of exercise as nearly uniform as possible each day.

**TYPE OF CASES STUDIED.** With this general program we find that 59.8 per cent of our patients have required insulin at the time of discharge from the hospital. We are aware that a small number have been able to discontinue using insulin within the few weeks following hospitalization. Also eventually some of those who did not need insulin at first find it required after months at home, so that these factors more or less counteract each other. Of far greater influence on the above finding is the type of diabetics who are referred to this hospital. Those who can be controlled by simple dietary restrictions without weighed diets are almost never sent to the hospital, since the clientele is very largely drawn from outside the city of Madison. Consequently the above per cent figure for insulin requirement is far higher than for the diabetics of any normal community. There were 252 males and 248 females in this series.

The age incidence of cases is shown in Table 1. The age at onset is often unknown. The figure used is age at the time of admission to this hospital, which is commonly within a few months of the discovery of the disease. There is perhaps nothing unexpected<sup>2</sup> in the age distribution of cases.

TABLE 1.—AGE INCIDENCE OF DIABETES AND OF COMPLICATIONS.

Decade.	Cases.		Pains, per cent.	Reduced reflexes, per cent.	Visual errors, per cent.	Gangrene, cases.
	Number.	Per cent.				
1 . . . . .	18	3.6	....	33	6	
2 . . . . .	62	12.4	5	45	32	
3 . . . . .	40	8.0	23	60	43	
4 . . . . .	51	10.2	35	47	45	2
5 . . . . .	74	14.8	46	46	46	4
6 . . . . .	110	22.0	46	39	41	12
7 . . . . .	107	21.4	41	45	37	21
8 . . . . .	38	7.6	53	61	32	11
Total . . .	500	100.0	35.8	46	38.4	50
Last 75 cases .	...	...	49	57.3	57.3	

**CAUSES OF DEATH.** The further data as to deaths suggest several features for attention. The 90 deaths do not give a fair picture of mortality of diabetes in our 500 cases, since we have been unable to secure recent replies to a large number of requests for information from patients. These 90 cases are of interest primarily for a study of the causes of death. In 76 cases the causes are reasonably well

known. One-half of these, 38, died in this hospital. It is immediately evident that diabetes is not the only cause of death, for one-third of the 90 did not require insulin when in the hospital. Similarly, 13 (34 per cent) of the 38 who died in the hospital did not require insulin even at the time of death.

In classifying the causes of death there is some duplication, since sepsis and coma are inextricably mixed in a few of the younger patients. The "neglect after training" group also includes cases appearing again under other heads, such as "coma." By this neglect is meant that the patient, or, too often, the parents, showed gross neglect in following the instructions given. This must be accepted as a challenge to more thorough training, and to a more elaborate effort to keep the patient in touch with some physician who can assist him in maintaining his morale. Perhaps the most important factor is the persuading of the home physician that he can properly supervise the case after hospital training. General practitioners still need to have available simple instructions for the management of diabetic patients.

Those patients in this group who died in coma suffered from either neglect or severe infections occurring outside the hospital. Coma can no longer be looked on as the great cause of death in diabetes who have been hospital-trained. Infection plays a far more serious rôle. In the septic group pneumonia and infected gangrene each explain one-third of the mortality. Pneumonia occurs throughout the age groups, relatively more frequently in youth. Gangrene deaths appear naturally in the later decades only. It is surprising that tuberculosis appears so infrequently as a recognized cause of death. Besides these 4 tuberculous cases, there are known only 4 others with this infection in the total of 500 cases, 1 convalescing, 1 moribund, 1 recently discovered and 1 not heard from.

Gas gangrene has occurred in only 3 cases during hospital care. In each case the condition arose in the operative stump after amputation of a leg for septic gangrene. In 1 case the patient was a farmer and skin contamination with anaërobic bacteria could be reasonably suspected as the source of the infection. In the other cases the circumstances seem explainable only as the development of blood-borne organisms in devitalized tissue. In none of these cases was further surgical treatment permitted after gas was recognized, and the cases were consequently fatal.

It is of interest to note the causes of death in the diabetics who have died in coma in this hospital. There have been only 5 of these in the entire period since insulin was made available. One was moribund at the time of admission, with sepsis in the leg and cardiac decompensation. Two others were critically ill with pneumonia, which probably induced the coma. Another, a child, was readmitted in coma occurring during measles, and died within an hour with extensive bronchopneumonia. One boy was admitted in

coma, with an indefinite history of head injury in addition to known diabetes. His acidosis and ketosis were completely relieved, but consciousness was not restored. Postmortem examination, regrettably not including the head, revealed no cause for death. All coma cases have been treated without the use of alkali. Alkali has not appeared necessary in any of our cases. In an earlier paper<sup>3</sup> evidence has been presented to show that insulin, carbohydrate and fluid may be depended on to make available alkali from the circulating acetoacetate in the diabetic with ketosis. We see danger in the general use of alkali, but use saline freely in the cases with acidosis and dehydration.

**CIRCULATORY SYSTEM.** It is not surprising that so many deaths are attributable to the cardiovascular renal disease triad. The deaths from this group occurred in the age range where the incidence of diabetes increases, presumably from the arteriosclerotic process itself. The numerical magnitude of this group of deaths confirms the clinical impression that the efficiency of the circulatory system is a consideration of prime importance in the management of diabetics. Further evidence is secured from the frequency of gangrene in diabetics. (Table 1.) Ten per cent of all of our cases had gangrene at some time. Healing occurred in most of these. Since the treatment of arteriosclerosis and of myocardial diseases is not on the specific basis which obtains for diabetes, the circulatory system is often neglected. This neglect, due to pessimism, is not justified by the experience of those who carefully adjust the program of exercise and medication to individual needs. Again there are many physicians who feel that diabetes of arteriosclerotic origin is benign. This is usually true in the sense that it does not often lead to marked acidosis and death in coma. Such patients are most apt to die from vascular accidents, including gangrene, cardiac failure or pneumonia. But such reasoning should not lead to careless handling of the diabetes. The most important single factor in the integrity of the circulation is the power of the heart muscle. Muscle weakness in general, myocardial weakness included, is a feature of marked diabetes. Adequate diabetic therapy restores muscle power and endurance. The very presence of cardiac difficulty is, therefore, added reason for meticulous effort to obtain the best results in diabetic management. Individual results in restored capacity for work frequently corroborate this point of view. We have seen no reason to modify our plan of dietetic treatment for older patients because of the presence of arteriosclerosis. There is no evidence that high fat diets tend to produce sclerosis.

**NEUROLOGIC COMPLICATIONS.** Examination of the case histories of these 500 patients was made to determine the frequency of such disturbances as pains in the extremities, reduced patellar reflexes and transitory visual disturbances. (Table 1.) In many of the records no specific mention is made of one or more of these matters, hence the incidence of the phenomena in question is probably some-

what higher than the data indicate. During the latter part of the eight-year period involved more specific questions and examinations were used, since these complications had been found to be of surprising frequency. There is no sharp time limit for this change, hence all the records are included.

It has been impossible thus far to make any differentiation from the histories between pains due to "neuritis" and those associated with vascular disease. The impression gained is that a neuritis is far less common than paresthesia, hyperesthesia, cramp pain and aches of vague type. It is rare to find the sensory disturbance limited to any one or several distinct nerve supplies. Consequently all pains in extremities, without obvious causes such as arthritis, infection or trauma, are included in the group which numbers 35.8 per cent of all cases. This figure would be somewhat larger if early histories were more adequate in disclosing minor pains, or those to which patients had become accustomed. Such pains were present in 49 per cent of the last 75 cases studied. It has been necessary to use analgesic drugs for the relief of such pains in only a few cases. We have tried the alternate warm and cold applications to the legs with some success, and with only a few inconsequential bullous lesions from the heat employed. But the use of the Buerger passive exercises for the legs<sup>4</sup> has in most cases been of real symptomatic help. The relief from pains frequently does not become evident until the exercises have been used for three or four weeks. The age incidence of these pains, as shown in Table 2, indicates the probability that they are related in part, at least, to the vascular deficiency incident to sclerosis. Leg pains in the second and third decades are commonly of the cramp type and are promptly relieved when diabetic therapy is adequate.

TABLE 2.—CAUSES OF DEATH OF 76 DIABETICS.

Decade.	Deaths.	Neglect.	Coma.	Cardio-vascular renal disease.	Carcinoma.	Septic processes.			
						Total.	Pneumonia.	Tuberculosis.	Post-gangrenous.
1 . .	6	2	4	...	...	3	3		
2 . .	7	4	4	...	...	3	3		
3 . .	7	1	1	...	...	5	2	2	
4 . .	7	2	1	2	...	3	1	1	
5 . .	8	1	...	1	...	6	1	1	1
6 . .	23	...	1	4	1	9	2	...	3
7 . .	21	...	...	10	1	13	3	...	7
8 . .	11	...	...	3	1	4	1	...	4
Total .	90	10	11	20	3	46	16	4	15

The reduced or absent patellar reflexes have seldom been mentioned as a characteristic of diabetes. From the incidence of 46 per cent here shown it may be stated with confidence that careful

examination will reveal this disturbance of nervous function in a majority of diabetics, excluding only the very mild cases. The histories from which the above data are taken were in many cases inadequate to differentiate between normal and reduced intensity of reflex response. During the last four years the records show lively reflexes as 2+, reduced reflexes as 1+ and entire absence of the response with reënfacement as 0. Their entire absence is seen in a small group of cases, without evidence of luetic infection. In the last 75 diabetics examined reflexes were reduced or absent in 57.3 per cent. Inspection of the individual records in the matter of pains and reduced reflexes shows that there is no marked correlation between these two matters. Either occurs frequently without the other. In a few cases in young patients we have observed acute loss of reflexes to be followed by a return within a few weeks after treatment became established. From the results of Woltman and Wilder<sup>5</sup> we might expect the frequency of reflex disturbance to show an age incidence similar to that for pains. It is evident that the reduction of reflexes is far commoner in the first four decades than is pain. We assume that this means a disturbed plane of nutrition of the nervous tissue due to the diabetic process, in addition to which a sclerotic factor becomes common in older patients.

**VISUAL ERRORS.** The data on optic symptoms include all cases which reported amblyopia, scotomata, diplopia or decreased visual acuity which became marked at approximately the time other evidence of diabetes appeared. As far as possible cataract cases are not in this group, except where there was evidence of improvement in visual acuity without surgical attention to the eyes. In this matter again some cases are necessarily included in which the symptoms are not due to diabetes, and many are omitted because of the failure to ask specific questions in the original history-taking by students or interns. Whereas there were only 38.4 per cent of such visual defects in the whole series of 500, the last 75 cases reported difficulty in 57.3 per cent.

A surprising factor is the large number of cases with visual symptoms in patients of the first four decades. The records are inadequate to reveal the frequency with which good function was regained. It is now our expectation, based on the experience of the more recent years in this series of cases, that visual function will show a marked return toward the previous level of acuity. It is not uncommon to have patients find that they cannot read newspapers during the first week in the hospital, but that within two weeks vision is as good as usual. Refraction had been done in some cases, with satisfactory result until the diabetes was discovered and brought under control. Then vision rapidly altered to such an extent that lenses were a handicap, and no clinical refractive error existed. The more intimate details of this refractive change are now being studied. It is possible to say that the change is not only simply one of blood-sugar concentration or of ketosis, although



both these may be factors. There is a gradual progressive return of visual acuity which often takes more than two weeks to be complete. It is our practice to avoid fitting lenses until the patient has been free from glycosuria for a four-week period. We hope to make a further report on the significance of these eye changes under treatment.

**FAMILY HISTORY.** In 20.4 per cent of these 500 cases a history of one or more diabetic members of the family was obtained. This figure obviously underrates the occurrence of other familial cases, since often only a casual question was asked, and inquiry at a later date might have secured information not available at the time of the first questioning. In 4 of the total series there was conjugal diabetes, that is, two couples were mildly diabetic (they were also obese).

**KETOSIS BEFORE TREATMENT.** Regardless of whether ketosis in the diabetic is held to mean inadequate fat oxidation or incomplete conversion of fat to carbohydrate, the occurrence of acetone bodies indicates severe diabetes. This can be evaluated in a prognostic way. We use the nitroprussid test without reinforcement by ammonium sulphate. Of our 500 cases there were 60.4 per cent who showed positive acetone tests at the time of admission. Following the dietary scheme outlined above, it was found necessary to use insulin at the time of discharge from the hospital in 84.4 per cent of this group of ketotic patients. Of the remainder of the cases which showed no ketosis on admission, it was found that insulin must be given according to the same criteria in only 22.2 per cent. Stated in other terms, when a patient is first examined and found to be diabetic, ketosis means that the chances are more than 5 to 1 that he will have to use insulin. If ketosis is not present the odds are almost 4 to 1 that insulin will not be needed. This early prognostic sign is of use in planning treatment, for if insulin is to be used it may as well be begun early to avoid delay. If it need not be used that knowledge is encouraging to the patient. The absence of ketosis may also be taken as evidence of relatively mild diabetes, and may, therefore, justify the postponement of a hospitalization for intensive treatment pending a trial of less marked dietary restrictions. Conversely the occurrence of ketosis should be taken as reason to insist on immediate and thorough efforts to meet the situation.

It is of some interest to examine the records of those nonketotic cases who nevertheless used insulin. There were 44 such cases. Six of these were given insulin for the definite purpose of shortening the hospital stay. In an unknown number of others the same factor was operative in part. Not infrequently improvement took place to such an extent that insulin was dispensed with. (This is occasionally true also of those cases with initial ketosis.) There were 3 thyrotoxic patients and 5 with infections of some magnitude included in the group of cases without ketosis who were given

insulin. Two-thirds of the remaining cases were over fifty years of age, and the insulin dosage was usually under 25 units per day. Only 5 cases of this group of 44 were given more than 25 units of insulin per day. It is evident, therefore, that the absence of ketosis is almost complete assurance against the need for insulin, unless there is such a complication as thyrotoxicosis or sepsis.

**Summary.** The study of the records of 500 diabetic patients seen in one institution in the eight years since insulin was made available shows that 60 per cent used insulin at discharge. Incidence of the disease and of 90 deaths is given by age decades. The causes of death include sepsis, cardiovascular renal disease and coma, in order of importance, as given. Gas gangrene occurred only three times. Pyogenic infection after gangrene and pneumonia are the commonest septic processes leading to death. Tuberculosis is infrequent. The significance of cardiovascular renal disease in the diabetic is discussed.

Pains in the extremities were found in 36 per cent and reduced or absent patellar reflexes in 46 per cent of the cases. Transitory visual disturbances were noted in 38 per cent.

The occurrence of ketosis at the time of admission or first examination is shown to be a good evidence of the need of insulin. Absence of ketosis is an equally reliable indication that insulin will not be needed.

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## ANTIANEMIC INFLUENCE OF DESICCATED WHOLE HOG STOMACH.

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In 1926, Minot and Murphy<sup>1</sup> published their epochal observations of the favorable influence of a diet rich in liver tissue in the production of a continued remission in cases of pernicious anemia.

More recently, Sturgis and Isaacs<sup>2</sup> and Sharp<sup>3</sup> have announced that whole chopped hog stomach, desiccated and defatted with petroleum benzine, contains an antianemic factor quite comparable to that contained in liver.

The remarkable experiments of Castle and Locke<sup>4</sup> indicate that an antianemic enzyme-like substance is absent in the stomachs of persons with pernicious anemia. By feeding the incubated contents of a normal human stomach, recovered about 1 hour after the ingestion of raw beef muscle, to patients with pernicious anemia, Castle and Locke produced a reticulocyte response, an increase in erythrocytes and general clinical improvement, comparable to that which follows liver treatment. Patients with pernicious anemia to whom only finely divided raw beef muscle was fed experienced no improvement.

Conner<sup>5</sup> and Wilkinson<sup>6</sup> found that the ingestion of either raw or dried stomach gives essentially the same results. Renshaw,<sup>7</sup> Rosenow,<sup>8</sup> Snapper and Dupreez,<sup>9</sup> Meulengracht and Hecht-Johansen,<sup>10</sup> Hitzenberger,<sup>11</sup> Geuting,<sup>12</sup> Jagić and Klima,<sup>13</sup> Gödel,<sup>14</sup> Holbøll,<sup>15</sup> Decastello,<sup>16</sup> Leschke,<sup>17</sup> Faber<sup>18</sup> and Wingé<sup>19</sup> have found that stomach therapy produces a prompt and lasting remission in cases of proved pernicious anemia. The therapeutic value of desiccated hog stomach tissue in pernicious anemia appears to be due to its ability to replace the absent enzyme-like blood-maturing substance in the stomach which normally acts as a constant stimulant to the blood-forming tissues.

In September, 1929, Dr. Cyrus C. Sturgis, of the University of Michigan, asked the writers to carry out an independent study of the therapeutic effect of desiccated hog stomach in cases of pernicious anemia, for the purpose of comparing results obtained at the Simpson Institute for Medical Research at Ann Arbor with those obtained in Dayton. During the past 18 months we have treated 15 patients with desiccated hog stomach,\* with results which appear in Table 1, p. 321.

An inspection of this table will reveal the fact that desiccated hog stomach was effective in producing a satisfactory remission in every case. The most striking clinical and hematologic results were obtained in those cases in which the red blood cell count prior to treatment was below 2,000,000. The reticulocyte response was inversely proportionate to the initial red blood cell count; in the cases in which the first red blood cell count was very low (1,000,000 to 2,000,000) the reticulocyte response was greatest (23 to 41 per cent). In this respect the response to stomach therapy is similar to that observed following the ingestion of liver or liver extract.

Of particular importance is the observation that certain patients

\* The material used (Ventriculin, N. N. R.) in the treatment of the first 10 patients was supplied, without cost, by Dr. E. A. Sharp, of Parke, Davis & Co., under whose direction it had been prepared.

with pernicious anemia who respond only to a moderate degree to liver therapy respond more favorably to stomach therapy. This was demonstrated in 2 of our cases (Nos. 14 and 15). Allerton,<sup>20</sup> Stokes,<sup>21</sup> Leschke,<sup>17</sup> Renshaw,<sup>7</sup> Snapper and Dupreez<sup>9</sup> and Isaacs, Sturgis and Rennie<sup>22</sup> have reported similar experiences in which the disease was but little influenced by liver or apparently potent liver extracts, but in which the substitution of dried stomach induced rapid subjective and hematologic improvement. Bertram<sup>23</sup> gave stomach powder to 11 patients with pernicious anemia; 10 responded favorably. In 1 case the stomach preparation was ineffective, whereas liver gave favorable results; Bertram assumes that this single failure might have been due to insufficient dosage. It is quite conceivable that occasional patients who do not respond to stomach therapy will respond to liver therapy.

TABLE 1.—RETICULOCYTE AND ERYTHROCYTE RESPONSE OF PATIENTS WITH PERNICIOUS ANEMIA TO DESICCATED WHOLE HOG STOMACH.

Patient No.	Before treatment.		Maximum per cent reticulo-cytes.	Days of treatment.	After treatment.	
	Red blood cells per c.mm.	Hemoglobin, per cent (Dare).			Red blood cells, per c.mm.	Hemoglobin, per cent (Dare).
1 . . .	940,000	20	36.4	62	3,810,000	78
2 . . .	1,240,000	30	31.0	58	4,320,000	82
3 . . .	1,260,000	29	27.0	69	4,040,000	84
4 . . .	1,330,000	33	29.7	60	4,840,000	88
5 . . .	1,460,000	30	24.6	85	5,100,000	86
6 . . .	1,540,000	41	16.6	124	4,080,000	76
7 . . .	1,690,000	48	41.0	48	4,050,000	82
8 . . .	1,750,000	40	23.0	56	4,800,000	86
9 . . .	1,760,000	40	17.6	53	4,340,000	80
10 . . .	1,850,000	30	11.0	44	3,740,000	68
11 . . .	1,960,000	40	15.8	72	4,810,000	79
12 . . .	2,080,000	48	15.9	63	3,240,000	74
13 . . .	2,430,000*	63	9.1	81	3,920,000	85
14 . . .	2,840,000†	58	3.9	84	4,510,000	86
15 . . .	2,940,000‡	57	3.4	98	3,870,000	80

\* Discontinued stomach therapy for 1 month, during which time erythrocyte count dropped approximately 1,000,000.

† Count following 3 months of liver therapy.

‡ Count following 7 months of liver therapy.

Of the first 10 patients studied, 5 were given dilute hydrochloric acid in rather large amounts (1 dram in plain tea, to be sipped during each meal) in conjunction with the stomach therapy, while the other 5 patients were given no dilute hydrochloric acid. The addition of dilute hydrochloric acid was apparently without effect, and has not been employed since that time. All of the patients in this series showed a complete absence of free hydrochloric acid in the gastric content. Repeated gastric analyses during the course

of the dried stomach treatment showed no return of free hydrochloric acid.

Transfusion was done in 1 case just prior to the institution of stomach therapy, without appreciable benefit. The clinical improvement following the ingestion of desiccated stomach in this case was most striking. The advent of liver extract or desiccated stomach appears to have eliminated the need for transfusions in patients with pernicious anemia. In patients who are moribund, the introduction of desiccated stomach through a stomach tube appears to be more effective than transfusion.

With two outstanding exceptions, we found 30 gm. of desiccated stomach to be the optimum amount to be given each day to persons with initial red blood cell counts below 2,000,000. For practical purposes, Sturgis and Isaacs have adopted the dosage of 10 gm. of the dried powder for each million deficit in the red blood cell count (using 5,000,000 as the standard).

The 2 exceptional cases were patients of advanced age (68 and 74 years). In both instances the daily administration of 30 gm. of desiccated stomach for a period of 10 days was practically without influence upon the number of reticulocytes or red blood cells. By increasing the dosage to 40 gm. a day, a characteristic reticulocyte response and a progressive increase in the number of red blood cells resulted.

We encountered no difficulty in administering the dried stomach powder. Tomato juice appears to be the most acceptable vehicle, although any of the fruit juices may be used. The powder is insoluble in any of these substances, consequently it is necessary to make a uniform suspension of the powder in approximately a cupful of whatever liquid is employed. This is best done by stirring the powder into the liquid with a large spoon in a bowl. It seems advantageous to give the entire amount at one time each day. None of our patients has complained of any objectionable taste, nor has there been any aversion to continued use of the stomach preparation.

For practical purposes, we have adopted a single dose of 10 gm. daily as a maintenance dose after the red blood cell count has reached approximately 5,000,000. Certain patients are able to continue in a remission with 40 to 60 gm. per week. To determine the final maintenance dosage, individual study is necessary. It is important to impress upon the patient at the outset of the course of treatment the necessity of continuing the treatment for the balance of his lifetime.

**Clinical Course During Treatment.** The most striking feature of the treatment is the almost dramatic subjective improvement which occurs within the first 4 or 5 days following the initial administration of adequate amounts of the stomach powder. The anorexia, languor, mild fever, abnormal bowel movements and gastric distress rapidly

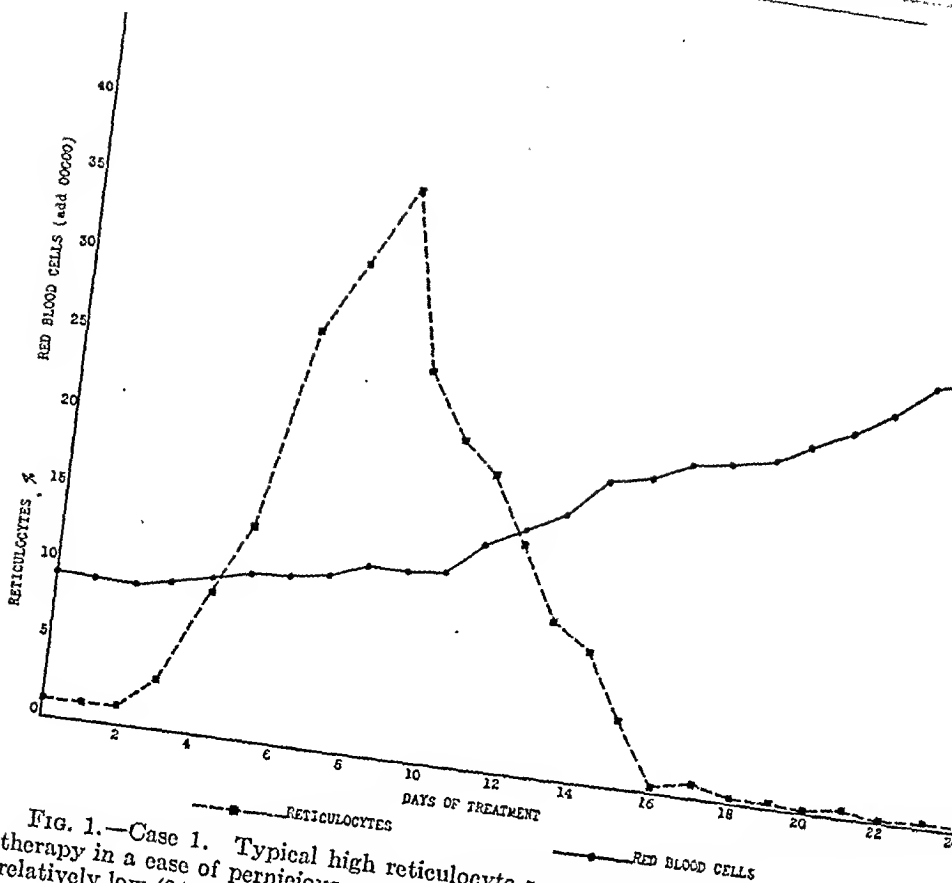


Fig. 1.—Case 1. Typical high reticulocyte response (36.4 per cent) to stomach therapy in a case of pernicious anemia in which the initial red blood cell count was relatively low (940,000).

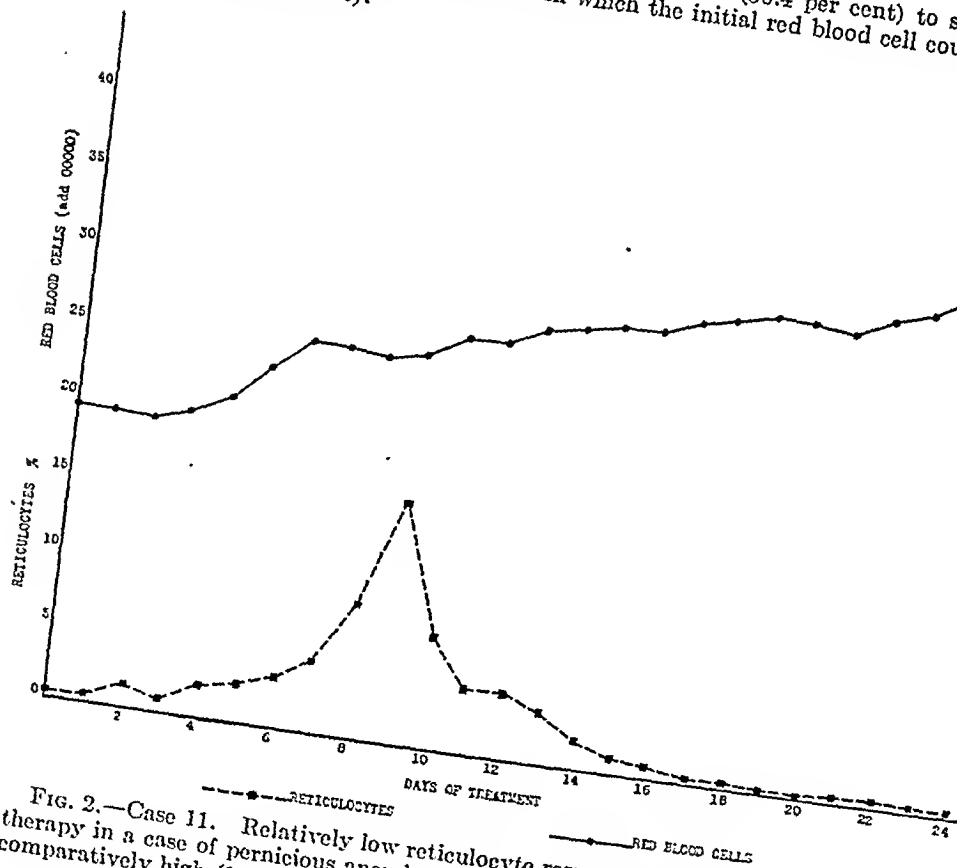


Fig. 2.—Case 11. Relatively low reticulocyte response (15.8 per cent) to stomach therapy in a case of pernicious anemia in which the initial red blood cell count was comparatively high (1,960,000).

disappear. The subicteric pigmentation of the skin and the marked pallor are gradually replaced by a more normal pink color, usually first observed in the skin over the pads of the distal segments of the fingers and toes, the skin of the palms and soles, the tip of the nose, chin and patches on each cheek. These skin changes usually occur before there is any significant increase in the red blood cell count or in the amount of hemoglobin, which probably indicates an early vasomotor influence.

If the neurologic manifestations of the disease are mild, consisting only of numbness and tingling of the hands and feet, these annoying symptoms will usually disappear, or be distinctly alleviated, within the course of a few days or weeks. Difficulties in locomotion due to loss of sensation in the joints are usually overcome to some degree. If the combined degenerative changes of the spinal cord are marked, to the extent of urinary and fecal incontinence, with the almost inevitable concomitant cystitis, little or no improvement of these more profound neurologic symptoms will occur. Five of our patients who had experienced numbness and tingling of the hands and feet for periods varying from 6 weeks to 5 months obtained complete relief from this annoying symptom; 3 others have experienced marked improvement. The neurologic manifestations of the disease have not progressed in any of our patients since the institution of desiccated stomach therapy. These observations lead us to conclude that it is imperative to maintain the erythrocyte count at the normal level in order to prevent further extension of preëxisting posterolateral sclerosis of the spinal cord.

The stimulating effect of the principle contained in desiccated stomach upon the hematopoietic system manifests itself about 3 to 5 days after treatment is begun by the production of a progressive increase in the percentage of immature red blood cells (reticulocytes). This wave of reticulocytosis usually reaches the crest from the seventh to the ninth day, after which the percentage of reticulocytes rapidly declines to the normal level. No significant rise in reticulocytes is to be anticipated if the erythrocyte count exceeds 3,000,000. The increase in mature erythrocytes usually begins during the reticulocyte rise and maintains a more or less steady increase of 400,000 to 500,000 per week. The determination of the percentage of reticulocytes each day during the first 10 or 12 days of treatment is of great value in that a satisfactory reticulocyte response indicates that effective blood regeneration is occurring.

If a patient who is thought to have pernicious anemia fails to develop a satisfactory reticulocytosis or other evidence of the anticipated remission following stomach or liver therapy, it is probable that one or more of the following factors is responsible for the failure: (1) Incorrect diagnosis; (2) inadequate dosage; (3) active infection; (4) impotent preparation; or (5) superimposed secondary anemia. The blood picture of pernicious anemia is occa-

sionally closely simulated by the anemia of syphilis, malaria, gastric or colonic carcinoma, hookworm or tapeworm infestations (particularly the broad tapeworm, *Dibothryocephalus latus*), hypothyroidism, aleukemic leukemia, splenic anemia, pregnancy and the puerperium, and the profound secondary anemia associated with prolonged chronic infection or dietary inadequacy. Sturgis and others have found that the presence of an acute or subacute infectious process may delay the reticulocyte response; as the infectious process subsides the red blood cell count usually progressively increases until the normal level is reached. Each new lot of the commercial preparation of desiccated stomach tissue (Ventriculin) is clinically tested and approved by the Simpson Memorial Institute, thus assuring a product of uniform potency. In the event of superimposed secondary anemia, iron therapy (ferrous carbonate, U. S. P., 2 gm. daily, or iron and ammonium citrate, U. S. P., 4 to 8 gm. daily) should be employed in addition to the stomach therapy.

**Summary and Conclusions.** 1. Desiccated defatted whole hog stomach in adequate dosage is effective in producing a prompt and continued remission in cases of pernicious anemia.

2. Occasional patients with pernicious anemia who do not respond completely to liver or its extract will obtain a more satisfactory response with stomach therapy.

3. The administration of dilute hydrochloric acid is apparently unnecessary in conjunction with stomach therapy. The advent of liver and stomach therapy appears to have eliminated the necessity for repeated transfusions in the treatment of pernicious anemia.

4. Certain patients of advanced age appear to require larger amounts of desiccated stomach for the production of an effective response than middle-aged patients.

5. We have encountered no patients who possessed an aversion to the continued use of desiccated stomach. The necessity for continuing adequate maintenance dosage throughout the remaining lifetime of the patient should be emphasized.

6. Mild neurologic symptoms disappeared or were distinctly alleviated in the 8 patients who experienced such symptoms prior to the institution of stomach therapy.

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## THE POSSIBLE CLINICAL INDICATIONS FOR FOLLICULAR HORMONE THERAPY BASED UPON ITS KNOWN BIOLOGIC EFFECT IN ANIMAL EXPERIMENTS.

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As a result of the international researches carried out in the last 10 years, it has now been firmly established that the female sexual cycle of warm-blooded animals is controlled by the interaction of

the hormones of the anterior pituitary and of the ovaries. In spite, however, of all the work which has been done, the exact nature of this mechanism in all its details is not yet clear. It is, however, definitely known that under the influence of the anterior pituitary the hormone is produced even in the ovaries of infantile individuals and, as a result, the female genital organs become mature and the secondary sex characteristics, both physical and psychologic, develop. Loewe was right in describing it as the hormone which confers the stamp of femininity, and since it is produced in large quantities at the time of maturation of the Graafian follicles, it is also called the "follicular hormone."

In view of the far-reaching effect of this hormone many investigators have thought it might be the only hormone produced by the female reproductive glands and therefore named it "the female sex hormone." However, it has now been shown that the ovaries must produce a second hormone in order to ensure the complete sexual function of the female organism. This is produced in the corpus luteum. Its function is to stimulate production of the decidua and thus prepare the uterus, which has proliferated under influence of the follicular hormone, for the nidation of the fertilized ova and to assure their further development.

**I. Chemistry of Follicular Hormone.** The follicular hormone was first obtained in the crystalline form by Doisy from the urine of pregnant women. Butenandt considers that chemically the hormone is a triple unsaturated oxyketone, probably of the stearin series, with the formula  $C_{18}H_{22}O_2$  (Fig. 1).

It is interesting to note that Marrian has isolated from the urine of pregnant women a second form of this hormone, with the formula  $C_{18}H_{24}O_3$  and considers this to be a double unsaturated trivalent alcohol (Fig. 2). His product "Æstrin," therefore, contains 1 molecule of water more, which is joined to 1 of the 3 double bonds of the first form. According to both Butenandt and Marrian, the efficacy of Æstrin is about one-fifth that of the hormone  $C_{18}H_{22}O_2$ . Whether Æstrin represents an excreted form of the hormone, for which there is considerable evidence, cannot be definitely stated at present; in any case Butenandt has succeeded in converting Æstrin into the more potent form by hydrolysis, a fact which establishes the structural relationship of the two forms of hormone. Commercial preparations produced from the urine of pregnant women may contain both forms side by side. Doisy has suggested the name Theelin for the crystalline hormone with the formula  $C_{18}H_{22}O_2$ .

**II. Action of the Follicular Hormone.** The effect of the follicular hormone is manifested in several ways: In castrated animals with extensive degeneration of the sexual organs and other physical and psychic changes, by the administration of the follicular hormone these changes may be prevented. Furthermore, in infantile female

animals a premature development of the sexual organs (Fallopian tubes, uterus, vagina, mamma) may be produced by means of the hormone.

In the following communication these effects will be described separately.

(a) *Effect on the Vagina.* The changes which the follicular hormone produces in the vagina of rodents is already well known since it constitutes the basis of the Allen-Doisy test. The introduction of the vaginal smear test by these two American workers has opened up a new and fruitful era in the progress of sexual hormone research.

The premature development of the infantile vagina into a sexually mature organ, which results from the administration of the follicular hormone *per os*, is shown in the accompanying illustrations (Fig. 3). Figure 3 shows a section through the vagina of an untreated infantile monkey (*Macacus rhesus*). The vaginal walls are in apposition and have but few folds; they are covered with a low pavement epithelium composed of four to eight layers and showing no cornification (Fig. 4). Figure 4 represents a section through the vagina of an animal of the same age which had been treated for a month with a total amount of 2000 rat units of follicular hormone. The lumen of the much-hypertrophied vagina is filled with horny epithelial cells. The epithelium itself is composed of many layers, the upper ones being mostly horny. The whole mucous membrane shows many fossae and folds. In the untreated animal the surface of the epithelium is parallel to the submucosa and only in a few places shows the formation of papillae, whereas the submucosa of the treated animal is thrust out in the form of papillary bodies. In the control animal the submucosa consists of dense and poorly-vascularized connective tissue. In the treated animal, on the contrary, the cells of the submucosa are loosely packed and there are many blood-vessels. There are abundant smooth muscle fibers in its outer layer.

(b) *Effect on the Uterus.* By the administration of the follicular hormone the uterus of an infantile castrated female can be brought to the same condition which it normally shows in the sexually mature animal during the first rupture of the follicles. This point will be discussed in greater detail in a later section in connection with the corpus luteum hormone. It will suffice here to briefly describe the appearance of the uterus in the above-mentioned experiments on infantile monkeys (Figs. 5 and 6). In contradistinction to the control animal, the uterus of the monkey which received 2000 rat units of follicular hormone is much larger and markedly more hyperemic. Whereas in the submucosa of the untreated animal there are only a few straight glandular tubules to be seen, numerous racemose tubules with high cylindrical epithelium can be observed in the submucosa of the treated animal. The endometrium of the untreated animal shows a single layer of low cylindrical epithelium, while the endometrium of the treated animal shows high cylindrical

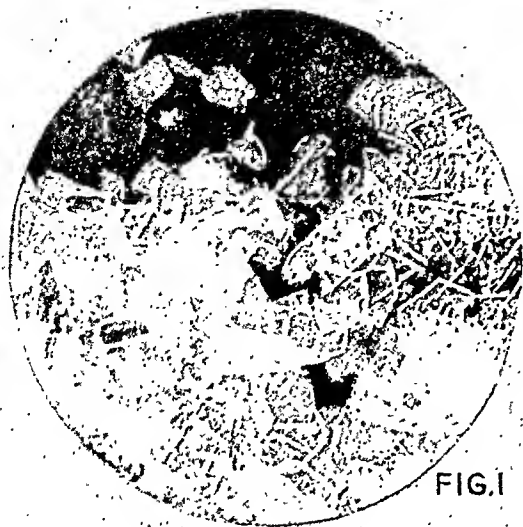


FIG. I

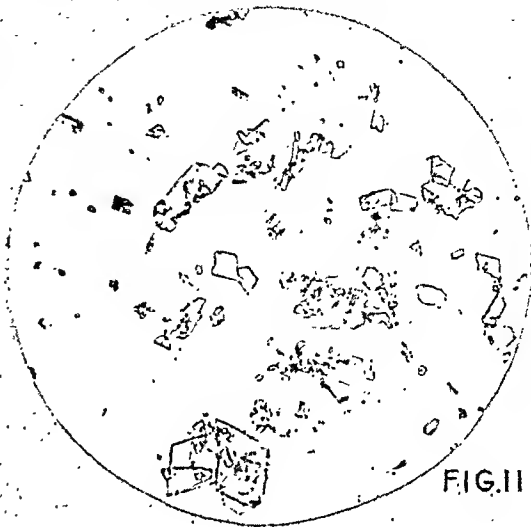


FIG. II



FIG. III

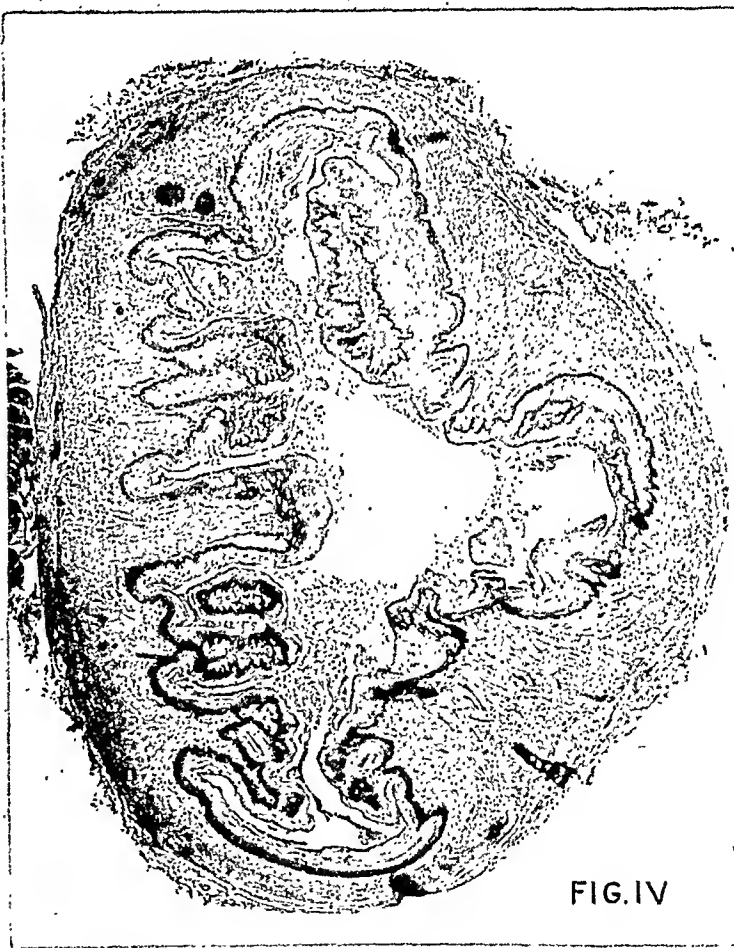


FIG. IV

FIG. 1.—Crystalline follicular hormone  $C_{18}H_{22}O_2$ ; 1 gm. = 8 million mouse units.

FIG. 2.—Crystalline follicular hormone  $C_{18}H_{24}O_3$  (Estrin); 1 gm. = 1.6 million mouse units.

FIG. 3.—Vagina of an infantile monkey.

FIG. 4.—Vagina of an infantile monkey after 4 weeks' peroral treatment with a total of 2000 rat units follicular hormone.



FIG.V



FIG. VI



FIG.VII

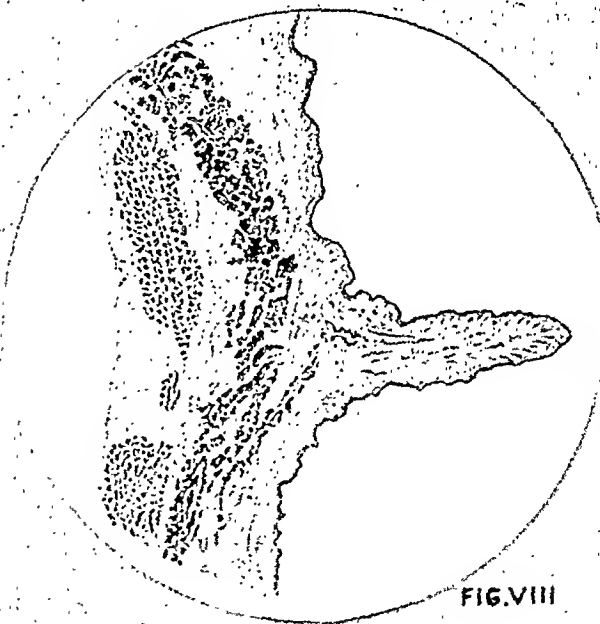


FIG.VIII

FIG. 5.—Uterus of an infantile monkey.

FIG. 6.—Uterus of an infantile monkey after 4 weeks' peroral treatment with a total of 2000 rat units follicular hormone.

FIG. 7.—Mamma of an infantile castrated guinea pig.

FIG. 8.—Mamma of an infantile castrated guinea pig after peroral treatment with follicular hormone.

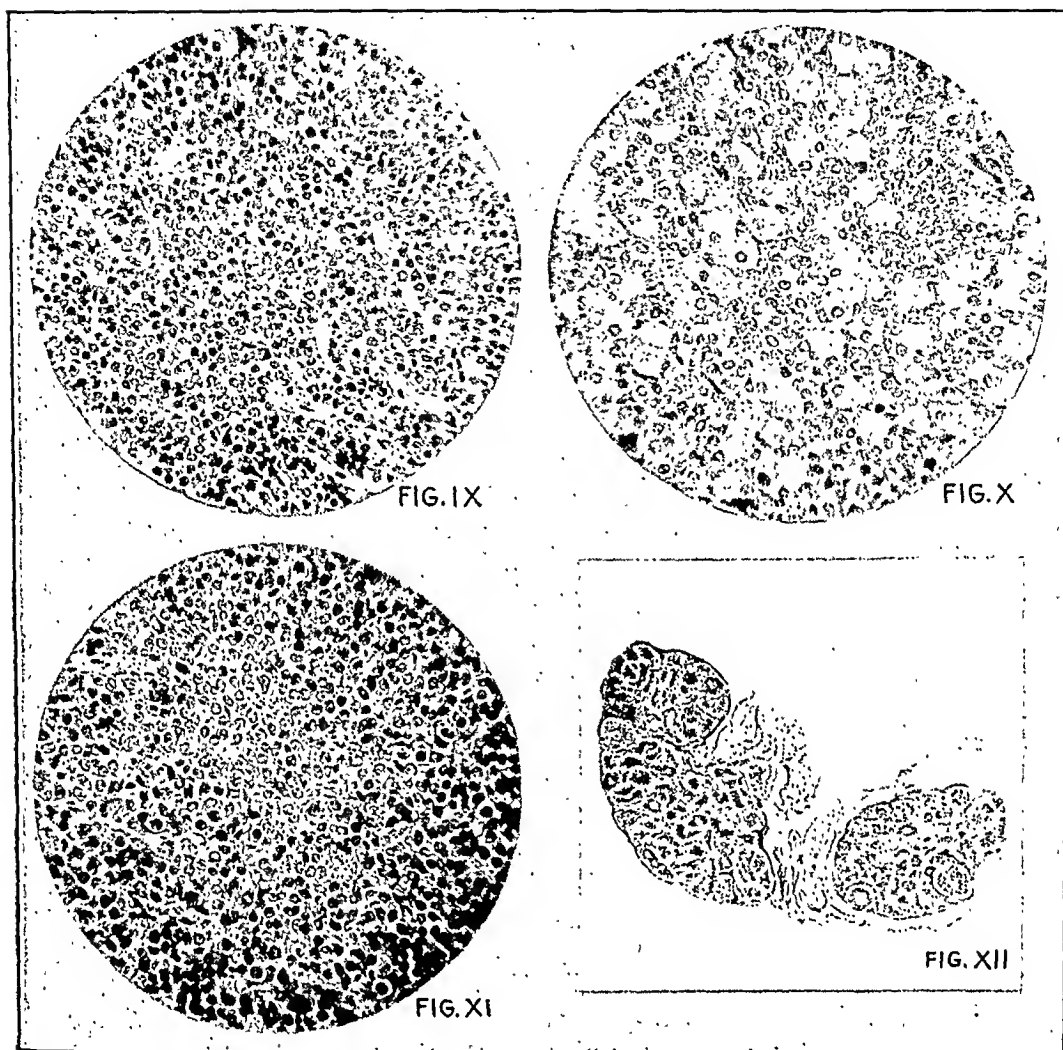


FIG. 9.—Anterior pituitary of an infantile female rat.

FIG. 10.—Anterior pituitary of an infantile female rat 3 weeks after castration.

FIG. 11.—Anterior pituitary of an infantile female rat which was treated with follicular hormone after castration.

FIG. 12.—Ovary of senile female rat removed before beginning follicular hormone treatment.



FIG. XIII

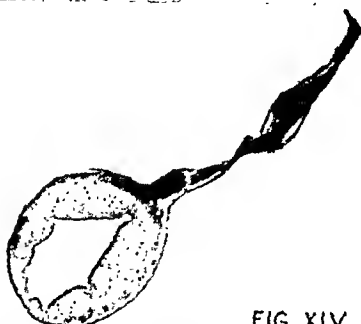


FIG. XIV



FIG. XVI



FIG. XV



FIG. XVII

FIG. 13.—The second ovary of the same animal 3 months after beginning follicular hormone treatment.  
 FIG. 14.—Uterus of an infantile rabbit.  
 FIG. 15.—Uterus of an infantile rabbit after treatment with physiologic doses of follicular hormone.  
 FIG. 16.—Uterus of an infantile rabbit after treatment with 1 rabbit unit of corpus luteum hormone.  
 FIG. 17.—Uterus of an infantile female rabbit, treated first with physiologic doses of follicular hormone and then with 1 rabbit unit of corpus luteum hormone.

cells. The hyperemic effect of hormone treatment is shown by the considerable increase in number and size of the bloodvessels in the parametrium of the treated animal. Robertson, Maddux and Allen obtained, by parenteral administration of about one-fifth of the peroral dose to castrated female monkeys, in principle the same effects.

(c) *Effect on the Mammæ.* The follicular hormone can also produce in the mammæ of infantile castrates a condition corresponding to that found in the adult mature female during the resting stage.

Figures 7 and 8 show sections through the mammæ of an untreated infantile castrated guinea pig and of its sister which had received the follicular hormone *per os* subsequent to castration. In the untreated animal the mamma and nipple is small and undeveloped. In the loose subcutaneous connective tissue isolated undeveloped glands are found lined with low epithelium. The superficial epithelium is undeveloped. The nipples are ill-defined. In the treated animal the whole mammary gland is much enlarged. The subcutaneous fat contains fully-developed clusters of tubules, the acini of which are lined with high epithelium. The superficial epithelium is higher and shows fully-developed nipples.

(d) *Effect on the Anterior Pituitary.* The formation of the ovarian hormone depends on the presence of the anterior pituitary hormone. The functional activity of the anterior pituitary is also modified to a certain extent by the hormones produced by the ovary.

Following castration marked changes occur in the anterior pituitary both in infantile and adult females, which can be made to disappear by treatment with follicular hormone (Figs. 9, 10 and 11). Figures 9, 10 and 11 clearly demonstrate this fact. This change in the anterior pituitary after castration and the possibility of preventing or reversing it by means of the follicular hormone can be used to determine the amount of hormone produced by the infantile ovary. In castrated infantile female rats the daily administration of one-thirtieth of a rat unit suffices to prevent the appearance of "castration cells" in the anterior pituitary, whereas a daily dose of one-fifteenth of a rat unit is enough to produce slight signs of rut. The amount of hormone produced by the infantile ovary must therefore lie within the above limits. Since the castration changes in the hypophysis correspond to a considerable increase in the production of the anterior pituitary hormone, and since the administration of follicular hormone is capable of reversing both the histologic changes and the increased functional activity of the anterior pituitary, it follows that the follicular hormone produced by the ovary exerts directly or indirectly a regulating influence on the hormone production of the anterior pituitary, whereby a hormonal equilibrium is maintained between the two glands.

(e) *General Effect.* The generalized changes (habitus, mental attitude) which occur after castration show that the reproductive glands have an influence on the body as a whole in addition to their



effect on the sexual organs. Possibly this effect is connected with the action on the whole endocrine system. Experimental proof of this generalized endocrine effect of the follicular hormone is well demonstrated in the work of Steinaeh, Kun and Hohlweg (*Pflüger's Arch.*, vol. 219, No. 2, p. 325).

The duration of individual "heat periods" in senile rats was controlled by daily vaginal smears and at the same time the body weight, percentage of hemoglobin and red cell count were ascertained. In these animals the heat cycle occurred at increasingly long intervals and finally ceased altogether. The body weight, hemoglobin percentage and red cell count slowly fell. Treatment with follicular hormone was commenced only when no "estral cycle" had been observed for several months. One ovary and part of a uterine horn were removed at the beginning of treatment. After an interval of a few days the senile animals were then injected with a sufficient dose of follicular hormone to produce a regular alternation of "heat" and resting periods such as is found in normal sexually mature animals. Four weeks after the commencement of treatment, growth of hair on previously bald patches, increase in weight and a higher red cell count and hemoglobin percentage were already definitely noticeable. After 2 to 4 months' treatment, when reactivation had made considerable progress (*e. g.*, increase in weight from 203 to 237 gm., increase of hemoglobin from 70 to 90 per cent and of red cells from 6.6 to 8.7 millions, within 3 months), the occurrence of antogenous "heat periods" was first observed after suspension of treatment. The prolonged administration of follicular hormone must evidently impart so strong a stimulus to the whole endocrine system that, as a result, the maturation of follicles and the formation of corpora lutea and the consequent production of follicular and corpus luteum hormones can take place in the ovary itself (Figs. 12 and 13). Figures 12 and 13 show the ovary of a senile rat before and after treatment with follicular hormone. The increased agility, higher metabolic rate and greater alertness of the treated animal are further indications of the general reactivation.

Changes in the distribution of the blood in the body can also be classed as a part of the general effects of the follicular hormone. K. Junkmann obtained the following results in a series of experiments on the action of the hormone on the gut. He found that it had no influence whatever on peristalsis in the isolated intestine. Also in rabbits treated with follicular hormone there is no difference in the behavior of the gut as regards peristalsis nor in its reactions to various excitant and inhibitory pharmacologic reagents, in comparison with the intestines of normal and castrated controls. On the other hand, there was a very marked hyperemia of the whole intestine of the animal treated with follicular hormone. It is conceivable that this improvement in the circulation would favorably influence spastic conditions which are due to a poor blood supply.

It will be seen, therefore, that apart from its direct effect on the sexual organs, the follicular hormone exercises a marked influence on the functional activity of the body as a whole, which influence is easily explainable by the close interdependence of the various units of the whole endocrine system.

(f) *Synergism with the Corpus Luteum.* According to our present knowledge the ovary produces the follicular hormone only until the time of sexual maturity, since it can be shown that complete development of the female genital system may be brought about by the artificial administration of the follicular hormone. Nevertheless, in order that it may be able to receive the fertilized ovum and to make possible the further development of the latter, the uterus must undergo a further change which consists in the formation of a decidua. This change is brought about by the hormone produced by the corpus luteum. Fraenkel has proved that the corpus luteum is an endocrine gland, the function of which is to bring about the implantation and further development of the fertilized ovum. Corner and Allen were the first observers to confirm this statement in experiments with corpus luteum extracts. Working in conjunction with us on a purified corpus luteum extract, C. Clauberg has closely investigated the combined action on the uterus of the follicular and corpus luteum hormones. As a result of our researches we found that unless the uterus has been brought to the normal condition of proliferation by means of physiologic doses of the follicular hormone, the corpus luteum cannot produce decidual changes in the uterine mucous membrane.

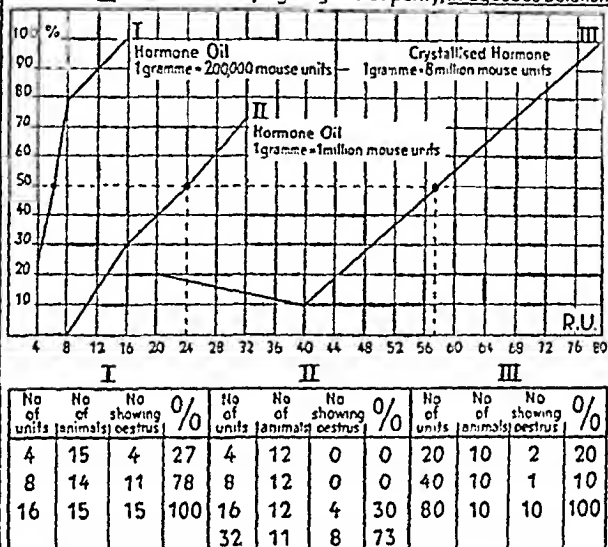
The normal proliferative dose for the uterus of the adult castrated rabbit was experimentally calculated by Clauberg to be 105 mouse\* units, which were administered in doses of 10, 15, 15, 20, 20 and 25 mouse units, spread over 6 days. Smaller or larger doses produce an insufficient or a pathologic proliferation respectively and it is then impossible to produce the normal decidual changes with the subsequent administration of corpus luteum hormone (Figs. 14, 15, 16 and 17). Figures 14, 15, 16 and 17 show the effect on the uterus of an infantile rabbit of separate and of combined treatment with follicular and luteal hormone respectively.

According to our present knowledge, menstruation in man represents the disintegration of the decidual mucous membrane of the uterus; we hope, therefore, that by means of combined treatment with physiologic doses of follicular and corpus luteum hormone, we shall be able to produce in a castrated woman the development of decidual changes in the uterine mucosa, which must finally result in the occurrence of menstruation. Clinical investigations directed to ascertaining the necessary physiologic dosage of the two hormones are at present in progress.

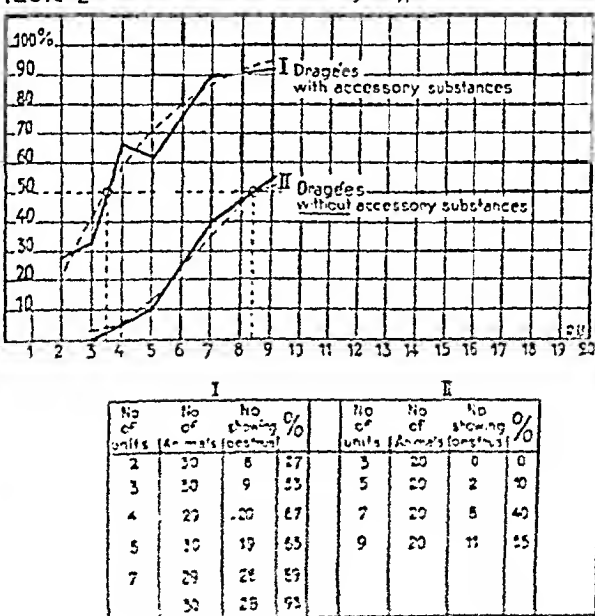
\* Five mouse units are equal to one rat unit.

III. Possible Methods of Administering the Follicular Hormone. The stability of the follicular hormone makes it possible to administer it not only parenterally, but also *per os*, *per rectum*, *per vaginam* and *via* the skin. Since apart from parenteral administration the most important method for therapeutic purposes is the peroral route, we carried out an extensive series of animal experiments on this

**Table 1** Hormone in varying degrees of purity, in aqueous solution



**Table 2** Emulsions of 2 different dragée types



point. The favorable results of peroral administration of follicular hormone are partly demonstrated in the foregoing illustrations. Particularly worthy of note, however, are the results of our experiments on the relation between the presence of certain concomitant substances and the effect of peroral administration (Tables 1 and 2). In Table 1 a comparison is made between the peroral effect of hormone products having a hormone content of 2.5 per cent, 12.5 per cent and 100 per cent respectively (in comparison with the crystalline hormone). *The crystalline product was by far the least effective.* In Table 2 the effectiveness of follicular hormone dragées with and without the addition of certain substances favorable to absorption, is shown. In the case of the dragées which were free from concomitants, 8.5 units were required to produce estrus in 50 per cent of the experimental animals, whereas in the dragées which contained concomitants favorable to absorption, only 3.5 units were sufficient.

It will be seen from the figures given in the tables that the preliminary experiments were carried out on a very large number of animals. Our subsequent experiments fully confirmed the results obtained. The necessary peroral dose of Progynon dragées showed a practically constant relationship to the subcutaneous dose of 4 to 1. These animal experiments would appear to justify the peroral administration of the hormone in human therapy.

**IV. The Therapeutic Outlook.** Animal experiments have clearly shown that the complete development of female characteristics in an individual is only to be expected when the follicular hormone is produced in adequate amounts. Follicular hormone therapy is, therefore, justifiable in all cases due to ovarian hypofunction.

Climacteric changes form the chief indication for follicular hormone therapy, and it will also favorably influence conditions due to partial or complete artificial suppression of ovarian function.

In this connection the relief of vasomotor disturbances, which form a frequent and distressing symptom, is most important. The symptom complex is not, however, confined to the cardiovascular system. Cutaneous manifestations such as pruritus and eczema, intestinal symptoms in the form of severe constipation, arthritic conditions which are refractory to antirheumatic treatment, are all met with and form a most favorable field for substitution therapy with the follicular hormone. Mental changes, especially the frequently-occurring psychic depression, are also benefited. Here the generalized tonic effect of the follicular hormone undoubtedly plays an important part since, in addition to readjusting local disturbances, it produces a condition of euphoria which is in full harmony with the somatic regeneration which successful hormone treatment produces in women. This general rejuvenation has also been observed in elderly women in whom the climacteric symptoms have already subsided.

Menstrual disorders which appear in the form of secondary amenorrhea, oligomenorrhea, dysmenorrhea, etc., constitute a further

indication for this therapy. In agreement with the experimental evidence of the effect of the follicular hormone on the whole endocrine system, clinical experience shows that the hormone is often capable of reestablishing a regular menstrual cycle. The many different forms which menstrual disorders may assume make it impossible for us to discuss the clinical aspect in detail.

Many cases in which follicular hormone therapy has proved a failure can often be explained on our knowledge of the mechanism of the physiologic action of the hormone which we have above described. For example, one cannot expect the follicular hormone alone to produce phenomena which are a function of its action combined with that of the corpus luteum hormone, which we have previously described.

Also, in cases of primary amenorrhea due to complete absence of development of the sexual organs, the administration of follicular hormone will be ineffective since it will find no adequate point of attack in the body.

It would also be fallacious to apply follicular hormone therapy in cases in which amenorrhea is the expression of a natural reaction to such conditions as advanced phthisis, cachexia, etc. Apart from these contraindications there is no danger attached to the employment of follicular hormone therapy.

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#### ABNORMALITIES IN THE WHITE BLOOD CELL RESPONSE. (LEUKEMOID, ATYPICAL LEUKEMIC AND LEUKOPENIC BLOOD PICTURES.)

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DURING the past 5 years there have been, on the wards of the Presbyterian Hospital, an unusually varied group of cases presenting abnormal white blood cell pictures. In many instances the type

of blood picture observed has not fulfilled the requirements for diagnosis. Because of the interest aroused in attempting to classify these changes and because of the difficulty in understanding the underlying situation, these cases have been collected. In this paper a selected number will be presented with the impressions that have developed.

The leukocytes usually respond promptly to the introduction of certain foreign agents into the body, whether these agents be relatively simple chemical compounds, or the complicated products of infection. Some of these foreign agents usually produce a leukocytosis, others a leukopenia. Many of these responses have been sufficiently observed and recorded that they have now been incorporated into our clinical conceptions as part of the expected and anticipated reaction in disease. Thus, a leukocytosis is expected in pneumonia, a leukopenia in typhoid fever, an eosinophilia in trichiniasis. These are considered as normal white blood cell responses to these infections.

Other less common leukocytic responses have also been observed and their clinical significance accepted. Young polymorphonuclear leukocytes, occasional myelocytes, and even rare myeloblasts are seen from time to time during the course of a severe infection. The presence of these immature forms is usually thought of as representing the output of an overacting, overstimulated bone marrow. The serious significance of leukopenia, occurring during the course of diseases usually associated with leukocytosis, is widely appreciated. We have recently come to view the syndrome known as glandular fever more as an unusual lymphocytic response to a transient throat infection than as a primary blood disease.

**Stimulation of Leukopoiesis.** The following cases are presented as examples of unusual responses on the part of the white blood cell elements of the hematopoietic system to stimulation. The cases are presented in order, beginning with mild transient abnormalities in the blood picture, proceeding to cases satisfying the present requirements for the diagnosis of leukemia.

**Case Reports.**—**CASE 1.** T. K., Unit 72505. A young clerk, aged 19 years, was admitted on July 8, 1928, for the repair of a right indirect, inguinal hernia. A blood count at this time showed a normal number of cells and normal differential. The hernia was repaired and the cord transplanted. His postoperative course was quiet except for a slight, persistent, unexplained temperature, thought possibly to be associated with a mild cough. He was discharged on July 29, 21 days after operation, in good condition, with normal temperature, with a small sinus in the wound.

After 3 days at home his temperature rose and he felt feverish and sick. He was readmitted on August 7 with a temperature of 104° F., pulse 120, definitely enlarged spleen, and tenderness and induration of the cord and right testis. His white count was 5800 with 70 per cent lymphocytes, no abnormal cells being seen. Blood cultures were negative and although the diagnosis of typhoid fever was considered, it was felt that his high fever was best explained by an acute orchitis. Five days later the white

count was 6600 with 72 per cent lymphocytes. The red count was normal throughout. Operation revealed an acute, suppurative, gangrenous testicle which was removed, with drainage of the infected area. The day after operation his temperature was 103.6° F., white blood cells were 10,900, 72 per cent lymphocytes. No abnormal cells were seen. His temperature rapidly returned to normal, as did the white count and differential. Ten days after operation, the white count was 10,600; lymphocytes, 32 per cent; polymorphonuclears 60 per cent. Culture of the wound grew *staphylococcus albus*.

This patient who was readmitted 1 month after operation with a high fever and strange white blood count presented a puzzling diagnostic problem solved only by exploration of the operative wound. It is of interest that a man, who, only a few weeks before, had a normal white blood count, should have developed this response to gangrene of the testicle.

CASE 2.—Dr. I. H., Unit 70074. A member of the house staff, aged 26 years, was admitted complaining of a mild gastrointestinal upset with a temperature of 101° F. On admission his only abnormal physical finding was a distinctly tender, easily palpable spleen. White blood cells, 9900; 75 per cent polymorphonuclears; 18 per cent lymphocytes; 3 per cent monocytes; 4 per cent myelocytes; and 1 per cent myeloblasts. The evening of admission he became chilly; his temperature rose to 102.4° F., and he complained of slight soreness of the throat and moderate drowsiness. His throat appeared normal but his gums were slightly red and boggy. There was no superficial glandular enlargement, but the spleen was still very tender. A white count taken at that time showed 7900 white cells, 74 per cent polymorphonuclears, 15 per cent myelocytes, 1 per cent myeloblasts. The following day he felt distinctly better. The temperature had fallen to 100° F. White cells were 9200, 79 per cent polymorphonuclears, 10 per cent myelocytes. Three days after admission his temperature was normal, he felt and looked well, tenderness of his spleen had largely disappeared, and his white cells had fallen to 4200 with 64 per cent polymorphonuclears and only 2.5 per cent myelocytes.

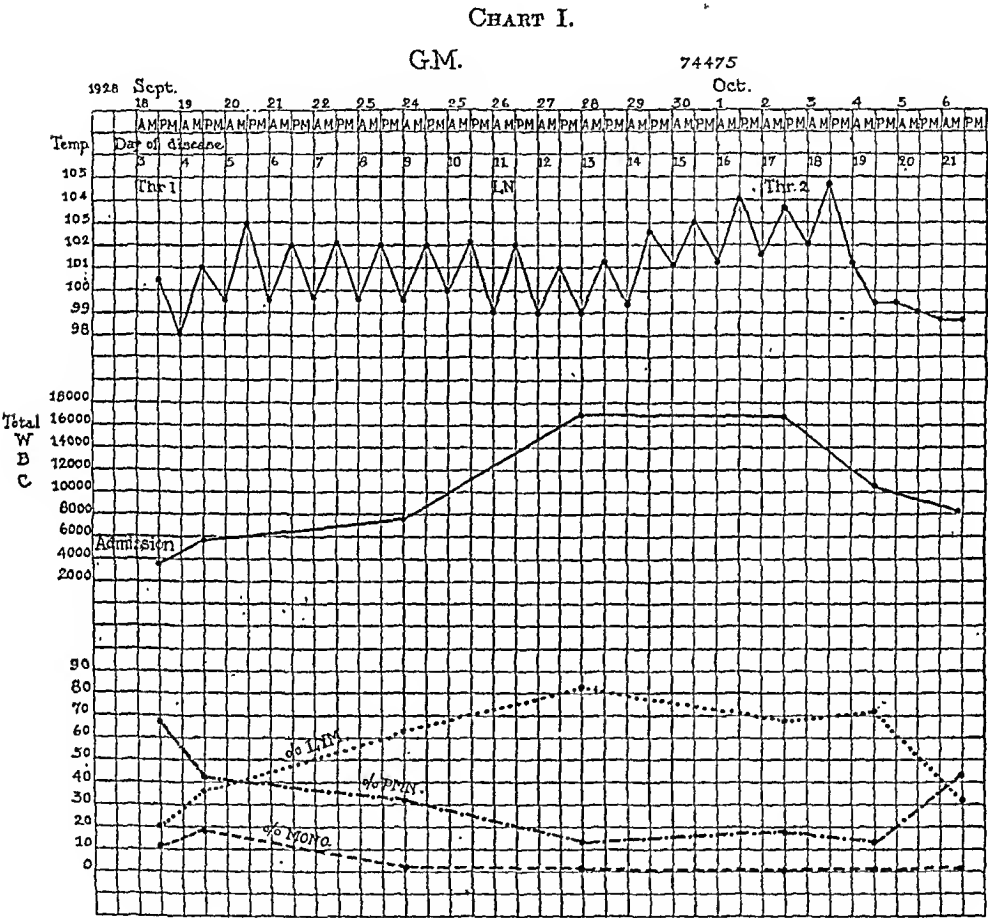
He was discharged on the day following and was without symptoms for 6 months when he developed a sore throat with generalized aches and pains, suggesting influenza. His white count at that time was 8500 with 10 per cent myelocytes. The tip of his spleen was palpable and slightly tender. The symptoms and abnormal physical signs rapidly disappeared. One week later the white blood cells numbered 10,000; polymorphonuclears, 63 per cent. No myelocytes were seen. He has now been well for over a year.

CASE 3.—E. C., Unit 70610. A negro housewife, aged 48 years, was admitted with a 6-day history of fever, cough, and pain in the chest. On admission there was a temperature of 102.4° F. and physical signs of pharyngitis and bronchitis. There was also a small aneurysm of the innominate artery, thought to be associated with the 4+ Wassermann. On admission she had a red count of 4,000,000; a white count of 36,000 with 85 per cent polymorphonuclears and 12 per cent myelocytes and myeloblasts. Three days later her symptoms had subsided, her temperature was normal, and her physical signs had disappeared. Her white count had fallen to 10,500; polymorphonuclears, 87 per cent; immature cells, 2 per cent. She was discharged a week later without symptoms, with a white count of 6800; polymorphonuclears, 78 per cent; lymphocytes, 20 per cent; monocytes, 2 per cent.

While under antiluetic treatment in the out-patient department, during

the 2 years since discharge, she has been examined at 6-month intervals and found normal.

CASE 4.—G. M., Unit 74475. An American salesman, aged 23 years, entered the hospital with a 3-day complaint of scattered aches and pains, mild chilly sensations, and fever. The admission diagnosis was gripe. Examination revealed a well-developed and well-nourished young man looking acutely ill. His throat was slightly injected and the cervical lymph nodes were moderately enlarged. The temperature curve and the white blood count are shown in the accompanying chart. (Chart I.) During the second week of his stay in the hospital, there was considerable further increase in



LN, appearance of enlarged lymph nodes. Thr., appearance of pharyngitis.

the size of the cervical lymph nodes, together with moderate enlargement of the axillary and inguinal nodes and spleen. At this time several whitish spots were observed on the posterior pharyngeal wall. These disappeared promptly after the return of temperature to normal. Two blood cultures taken during the febrile stage were negative.

He was seen in the medical follow-up 4 months after discharge from the wards, at which time he was without symptoms or abnormal physical signs.

This case probably represents a slight variation from the group of cases of glandular fever. The preliminary leukopenia, although



described in glandular fever, is not the usual white blood cell response in that condition.

Typical cases of glandular fever, conforming in all respects to the published descriptions, might be included at this point as further examples of queer leukocytic reactions to throat infection. Several examples of this syndrome have been seen, but, as this clinical picture is now so well established, it is felt that analysis of these cases would be unnecessary here.

The preceding cases represent relatively mild, transiently abnormal hematopoietic responses with prompt return of the blood picture to normal and recovery of the patient. The following cases show a more severe and progressively abnormal response of the hematopoietic system with ultimate death of the patient.

CASE 5.—M. H., Unit 54731. A school girl, aged 13 years, was admitted with an 11-day history of ulcerative stomatitis. Her past history was irrelevant except for the fact that she had been losing weight for a year. On admission she was acutely ill and showed ulcers of the buccal mucous membrane. Her red count was 2,000,000; hemoglobin, 45 per cent. Platelets numbered 11,000. White blood cells were 2400; 20 per cent polymorphonuclears, 17 per cent lymphocytes. Sixty-three per cent of the cells were immature forms thought to be myelocytes and myeloblasts. Oxidase stain showed that many of these abnormal cells contained granules. She became rapidly worse. Her gums became spongy and boggy. There were frequent nose bleeds. The lymph nodes and spleen, which at first were not enlarged, increased rapidly in size, became tender, and she died 10 days after admission with what was thought clinically to be an acute myeloblastic leukemia. Blood cultures were negative. Hemolytic and nonhemolytic streptococci were isolated from the ulcers in the mouth.

At autopsy an extensive, acute, caseating tuberculosis involving chiefly the lymph nodes and spleen was found, with terminal dissemination. The bone marrow was hyperplastic. There was no evidence of any kind of the changes found in acute leukemia. The final anatomic diagnosis was recorded as tuberculosis of the lymph nodes, spleen, liver, kidney, Fallopian tubes, and lung; gangrenous stomatitis and gingivitis; petechial hemorrhages of skin, pericardium and pleura; hyperplastic bone marrow. Morphologically typical tubercle bacilli were demonstrated in the microscopic sections.

CASE 6.—W. H., Unit 74853. A policeman, aged 57 years, was admitted complaining of progressive weakness, loss of 25 pounds in weight, an unproductive cough without fever, over a period of 1 month. He had also noticed progressive enlargement of his left upper abdomen. Physical examination showed a chronically ill man with obvious loss of weight, an enlarged liver extending 6 cm. below the costal margin, and a very large, hard spleen extending to the iliac crest. His red count was 3,400,000 with 65 per cent hemoglobin. White cells numbered 70,000, polymorphonuclears, 61 per cent; monocytes, 8 per cent; lymphocytes, 13 per cent; basophils, 8 per cent; with basophilic myelocytes, 3 per cent. There were 6 per cent eosinophils with 1 per cent eosinophilic myelocytes. There was moderate anisocytosis and poikilocytosis and marked polychromatophilia. He was admitted as a case of chronic myelogenous leukemia. Bleeding and clotting times were normal. There was no fever during the 3 weeks' stay in the hospital. He was then discharged to be followed in the out-patient department, receiving radiotherapy.

He was readmitted 5 months later complaining of weakness and a dry

cough of 2 weeks' duration. His temperature was 102° F. There was a slight dullness and diminished breath sounds over the left lower lobe posteriorly. Roentgen ray of the chest showed diffuse peribronchial infiltration radiating outward from both hila. His red count was 4,000,000. His white count had fallen gradually during the preceding months and was now 5500, 86 per cent polymorphonuclears, 8 per cent myelocytes, 6 per cent lymphocytes. There was an apparent increase in the number of platelets. It was felt that he had a lobular pneumonia and that the altered white count resulted from radiotherapy. His spleen was considerably smaller than on his previous admission, reaching but 7½ cm. below the costal margin. During the 3½-week stay in the hospital, he ran an irregular fever, reaching 104° nearly every day. Indefinite signs persisted in his chest. He lost ground rather rapidly and died. In spite of 2 transfusions, his white count just before death was 2160 with 76 per cent polymorphonuclears, 17 per cent myelocytes, 3 per cent myeloblasts. His final red count was 4,520,000. Platelets were still reported as increased. Blood cultures throughout his terminal illness were negative. His sputum grew out hemolytic streptococcus and was negative for tubercle bacilli on 2 separate examinations. At the time of death it was believed that he had a typical, chronic myelocytic leukemia with a terminal pulmonary infection, the nature of which was not determined, but which was thought, from the physical signs and Roentgen rays, to be a lobular pneumonia.

Autopsy revealed an extensive tuberculosis, involving chiefly the spleen and lymph glands, with an acute generalized miliary process and a tuberculous pneumonia. The process in the spleen appeared to be the oldest tuberculous lesion. Numerous tubercle bacilli were found in the microscopic sections. Nowhere could any lesion be found to indicate myeloid leukemia.

CASE 7.—H. S., Unit 70905. A chauffeur, aged 58 years, was first admitted in February, 1928, with a month's history of fever and pain in the chest. He had a mild secondary anemia. The white count on several examinations was within normal limits. No abnormal cells were seen. There were physical signs of a right pleurisy with effusion. Aspiration of the chest resulted in the unexpected presence of thick, foul pus from which an anaërobic streptococcus was isolated. Thoracotomy was performed and the cavity drained. He was discharged 3 months after operation, in satisfactory condition, and he returned to work.

He was readmitted in July, 1929, with a month's history of weakness and fever. Examination revealed at this time a sallow, anemic man without other abnormal physical findings. The red count was 3,000,000; hemoglobin, 65 per cent. White blood cells, 1900; polymorphonuclears, 20 per cent; lymphocytes, 72 per cent, and monocytes, 8 per cent. No abnormal or young forms were seen. The symptoms persisted and were accompanied by a moderate swinging fever, rarely rising above 101° F. The white blood count remained about as on admission, as did the red count, both being transiently elevated after transfusion. Two weeks after admission several slightly enlarged lymph nodes were observed, one of which was removed, sectioned and diagnosed as chronic lymphadenitis. Roentgen rays of the chest showed a moderate increase in the hilum lymph nodes and this, together with the weakness and the anemia, suggested the possibility of Hodgkin's disease. He was discharged on September 15, still undiagnosed and unimproved.

He returned on October 8, distinctly worse, but still without definite physical signs, except for the presence of a small amount of fluid in the left chest. Red count was 2,700,000, 55 per cent hemoglobin. His white blood cells had altered surprisingly and now numbered 13,000, 9 per cent polymorphonuclears, 48 per cent lymphocytes, and 43 per cent myeloblasts.

He was thought to belong to the group of leukosarcomata because of the leukemic type of blood picture and the presence by Roentgen ray of a rapidly increasing mediastinal tumor. He failed rapidly and died on the 23d of October.

At autopsy he was found to have the typical microscopic lesions of acute myeloblastic leukemia. In addition, it was found that the enlarged hilum lymph nodes were the site of extensive caseous tuberculosis with a terminal tuberculous pneumonia and generalized miliary dissemination. It was felt that the case probably represented one of chronic progressive tuberculosis of the hilum lymph nodes, spleen and other lymph nodes, with terminal spread, in which an acute myeloid leukemia had developed.

CASE 8.—V. B., Unit 227639. A Canadian bank clerk, aged 23 years, came in on November 6, 1929, with a 9-day history of mild cold and a 3-day history of high fever and a sore mouth and throat. There had been no chill or chest pains and no cough. His past history was irrelevant. He presented the appearance of a prostrated, dyspneic, desperately ill young white man. His temperature was  $105^{\circ}\text{F}$ .; pulse, 112; respirations, 34. His gums, tongue, buccal and pharyngeal mucous membranes were the site of a severe necrotizing infection. There were signs of lobular pneumonia in both lungs. Examination was otherwise negative. There were no petechiae. Repeated blood cultures and blood Wassermann were negative. He had a normal red blood count and hemoglobin throughout. His white count was 26,000 on admission and slowly fell to 11,000 4 days later when he died.

In all the smears there were many young polymorphonuclears and rare myelocytes. There were, in addition, between 15 and 25 per cent of large, definitely abnormal white cells. Some of these were thought to be embryonic monocytes, but most of them could not be classified.

Autopsy revealed a necrotizing infection involving the entire respiratory apparatus with early gangrene of both lungs. The bone marrow was hyperplastic and contained many young white blood cells, as did the spleen. It was felt by the pathologists that the case could not be definitely grouped as an acute leukemia, but that that condition was closely approximated. Cultures were unsatisfactory and Gram stains of the microscopic sections revealed many organisms, none of which could be identified as predominating.

Clinically this patient presented a rapidly spreading, necrotizing infection of the mouth, throat, and lungs. The presence of the large number of abnormal white cells, together with myelocytes and young polymorphonuclears suggested antemortem the possibility of a coincident acute leukemia. Postmortem, the hyperplastic bone marrow and the presence of many immature white blood cells in the spleen also suggested leukemia.

This case was classified by the attending physician and by the pathologic staff as a leukemoid type of reaction to a severe infection and not as an acute leukemia. Both groups, however, felt that the blood dyscrasia as well as some of the microscopic lesions strongly suggested the presence of true leukemia and that these pathologic changes very nearly satisfied the existing requirements for making that diagnosis.

CASE 9.—J. G., Unit 69160. An American stenographer, aged 20 years, who came in complaining of trouble with the teeth, bleeding and soreness of gums, increasing weakness and pallor of 6 months' duration. On admission she had a slight fever and was definitely pale. There were small superficial ulcers in the mouth; the gums were spongy and red. There were no

petechiæ but there was a small purpuric eruption over the leg. The tip of the spleen was just palpable. There was a slight enlargement of the cervical and axillary lymph nodes. On admission the red blood cells were 3,600,000, 75 per cent hemoglobin. White blood cells were 14,200, 85 per cent myeloblasts. Vigorous treatment of the lesions in her mouth and gums was immediately instituted. Three days after admission the white blood cells were 10,000, 60 per cent myeloblasts. The lesions in the mouth and gums showed improvement. A week after admission her white count had fallen to 6000 with 46 per cent myeloblasts. A week later further improvement was noted in the condition of her gums and mouth. At this time her white count was 3000, 75 per cent polymorphonuclears, 10 per cent lymphocytes, and only 1 per cent myeloblasts. Petechiæ which had appeared a week previously, disappeared temporarily at this time. Then quite suddenly the mouth lesions became very much worse. A severe ulceration of the gums set in. Her temperature rose rapidly and she died 4 weeks after admission. Her final blood count showed 20,000 white cells with 75 per cent myeloblasts and only 5 per cent polymorphonuclears. Blood cultures on 2 occasions were negative. Attempts to isolate the organisms from her gums were unsuccessful. No Vincent's organisms were found. The final clinical diagnosis was acute leukemia. Autopsy was refused.

The possible relationship between acute infectious mouth lesions and leukemia has often been suggested, and it is of interest here that the patient showed distinct, though transient, improvement in her general condition as well as a definite return of the blood picture toward normal during the time that her mouth lesions appeared to be responding to vigorous local therapy.

CASE 10.—M. L., Unit 79151. An American cashier, aged 58 years, was admitted with a 4-day history of abdominal pain, obstipation and frequent vomiting. On admission he was *in extremis*. His spleen was palpable 4 cm. below the costal margin. Physical examination was otherwise negative. Red blood cells numbered 4,000,000 with 75 per cent hemoglobin. Platelets were normal. White blood cells were 2700 with 75 per cent polymorphonuclears, 15 per cent lymphocytes, and 10 per cent monocytes. Blood culture was negative. He died shortly after admission with a clinical diagnosis of acute intestinal obstruction. At autopsy a very unusual streptococcus infection of the duodenum was found, causing obstruction at this point. Microscopically the liver showed marked periportal accumulation of lymphocytes, a picture identical with that seen in lymphatic leukemia. No other evidence of leukemia, however, was seen.

A case of rapidly fatal streptococcus duodenitis showing a depression in the total number of white blood cells without the presence of abnormal forms in the blood. The point of interest is that one of the standard anatomic requirements for the diagnosis of lymphatic leukemia was present.

CASE 11.—J. D., Unit 63220. A young American boy who was followed in the Presbyterian Hospital from the age of 2, when he was found to have chronic bronchitis, rickets, and hypertrophy of the tonsils. His tonsils were removed and for several years he was without symptoms, except for a mild persistent cough.

At the age of 8 he came in with a short history of abdominal pain and vomiting. There was considerable tenderness in the right lower quadrant and it was felt by the surgeons that he had a typical acute appendicitis.

The red blood cells at that time were normal but the white blood cells numbered 39,000, of which 42 per cent were polymorphonuclear, 14 per cent lymphocytes, 34 per cent monocytes, and 10 per cent myelocytes. This blood count was repeated with the same results. In view of the strange count, operation was withheld and the symptoms and signs of appendicitis slowly disappeared.

During the next 2 years he was never entirely well, did not gain weight as he should, and had persistent cough. He was closely followed during this period, his white blood cells ranging between 25,000 and 60,000, with a high percentage of monocytes and a small number of abnormal young cells on each examination.

He was admitted to the hospital several times for investigation. No definite diagnosis was ever made. It was felt by some that he had a chronic leukemia in view of the slow increase in the size of the spleen and lymph nodes, while others felt that the unusual blood picture was a reaction to a chronic infection, probably in the lungs, although no definite evidence of pulmonary infection could be found. He was given radiotherapy with slight decrease in the total number of white cells and marked decrease in the number of platelets, resulting in several moderately severe hemorrhages.

On his sixth admission to the wards at the age of 10, there was fever, nausea and vomiting of several days' duration. At this time there were no markedly abnormal physical signs and the red cells numbered 5,800,000, white blood cells 54,000. Dr. Florence Sabin examined the blood smear and reported a large number of monocytes which suggested to her a reaction to a chronic infection rather than a true leukemia. One of the cervical lymph nodes was removed and was found to contain scattered areas of tuberculosis. For several months it was felt that the blood picture was probably a result of the chronic low-grade tuberculosis of the lymph nodes.

During the final year of his life he became sicker and developed many scattered skin infections. The white count during the last 6 months of his life altered considerably with a progressive rise in the total number, reaching 324,000 shortly before his death, 57 per cent polymorphonuclears, 25 per cent lymphocytes, 8 per cent myelocytes, 10 per cent monocytes. The terminal event was the development of an empyema from which a non-hemolytic streptococcus was isolated. At the time of death no satisfactory explanation of the patient's illness during the 3 years that he had been under constant observation was forthcoming. It was felt that, with the terminal very high white count and the progressive anemia, he almost surely had a chronic leukemia.

At autopsy an old, foul-smelling abscess was found in the right lower quadrant in the center of which were the remnants of a ruptured appendix. In addition, there were the changes, both gross and microscopic, usually associated with chronic myeloid leukemia. There was no evidence of tuberculosis.

The final anatomic diagnosis was chronic appendicitis with perforation, chronic retrocecal abscess, and chronic myeloid leukemia.

A case of acute appendicitis 3 years before death with rupture and the formation of an abscess. During these 3 years the patient had a chronic suppurative focus about the appendix, and there was a progressive alteration in the blood picture thought to be, at first, a reaction to chronic infection, but simulating before death chronic leukemia.

*Autopsy* revealed for the first time this chronic focus. It also revealed the changes on which the diagnosis of chronic myeloid leukemia is anatomically based.

CASE 12.—H. P., Unit 66079. A young American school girl, aged 14 years, was suddenly taken with acute abdominal symptoms which proved to be due to a gangrenous appendix. At the time of operation, the blood showed the usual moderate leukocytosis with the relative increase in polymorphonuclear leukocytes. Although immediate recovery appeared to be satisfactory, the wound remained opened and infected. After 5 weeks the patient was readmitted, complaining of increasing weakness and pallor. Examination of the blood at this time showed a moderate secondary anemia with a decrease in the number of platelets. The white count was 15,000 with 88 per cent of large immature cells. There was a high temperature and a blood culture, as well as the wound culture, showed hemolytic streptococcus. Her temperature rose to 106° F. on the sixth day and she died. Just before death the white blood count in the peripheral blood had dropped to 2400 with many immature forms persisting. The clinical diagnosis of acute leukemia, associated with hemolytic streptococcus septicemia, was borne out by the pathology. The most typical leukemic infiltrations were found in the intraabdominal lymph nodes and in the liver. There had occurred in the tissue about the abdominal wound and in the cecal mucosa an unrestrained growth of streptococcus which completely suppressed a local inflammatory reaction. So far as could be told from the sections, there was no involvement of the regional veins, so that the infection of the blood stream must have occurred through the thoracic duct. It is of great interest that the leukemic lymph glands most evidently involved were those situated along the route of absorption from the abdominal wound.

These last two cases are being presented in detail by Dr. K. R. McAlpin and Dr. B. C. Smith.

**Discussion.** Until the nature of the leukemias and the leukemia-like states is more thoroughly understood, or until such time as experimental methods are devised for the accurate study of these conditions, as they exist in humans, our only method of approach is by the observation and analysis of clinical material. As previously stated, the cases presented here have been selected from a fairly large group and are presented largely for their clinical interest. Any conclusion that may be drawn from observation of material of this sort is at best indefinite, as it is based entirely on impressions. Exact statements cannot be made. Even the additional information derived in many of these cases from the study of the pathologic material is of only limited assistance. From the point of view of the pathologist, the diagnosis of leukemia rests largely on his definition of the term and is not based on any clear understanding of the nature of the disease. Certain stated requirements must be met to make the diagnosis possible. If these previously stated requirements are met, the diagnosis is accepted. If any of these stated requirements do not exist, another diagnosis must be substituted.

In all of the above cases, infection existed. Coincident with this infection there was a deviation in the white blood cell picture from the normal. In the earlier cases this deviation was relatively mild and transient and can be classified as the leukemoid type of reaction. In others, the infection was considerably more severe and the deviation of the blood picture from normal considerably more striking.

In this particular group, the diagnosis of leukemia could not be definitely made either clinically or anatomically, although that condition was often very closely approximated. A few of the cases satisfied both the clinical and the anatomic requirements for making the diagnosis of leukemia and are classified as such. In each case, there seemed to be a relationship between the infection and the blood picture.

The observation of leukemia and leukemoid blood pictures in close relationship to infection is not new. Several observers have attempted to establish infection as the etiologic agent in acute leukemia. The presence of leukemoid blood pictures in association with progressive tuberculosis has been observed and the existence of true leukemia and progressive tuberculosis has been recorded and is not, apparently, an uncommon combination.

The 3 cases of tuberculosis presented here possessed unusual interest in that the relationship between this infection and the abnormal blood picture seemed to be intimate. Case 5 presented the typical clinical picture of acute myeloblastic leukemia and no other clinical diagnosis was considered. If autopsy had not been performed, this case would undoubtedly have been accepted and recorded as a typical example of this blood disease. Autopsy, however, and study of the microscopic sections of the organs did not uphold the diagnosis of leukemia. Instead, an extensive caseating tuberculosis of the lymph nodes and spleen was discovered. This appeared to be a relatively acute process. It is impossible to do more than suggest that the clinical picture of leukemia may have been dependent upon the presence of this extensive tuberculous infection. Case 6, with its markedly enlarged spleen and very high white count, was accepted clinically as an example of chronic leukemia. The presence of abnormal white blood cells in the smear supported this clinical diagnosis, as did the general course of the disease. The presence of the tuberculosis found at autopsy was not suspected before death and again it is felt that perhaps the unusual blood picture presented by this individual may have been dependent upon this progressive infection. Case 7 presented, during life, many features in common with Case 5. Both died with what was clinically acute myeloblastic leukemia. In the former instance, the diagnosis of leukemia was not upheld by autopsy. In the latter instance, the specified requirements for making that diagnosis were present and that diagnosis was made. Whether or not any fundamental difference existed between these 2 cases cannot be stated. The similarity between them during life was so striking and, as the pathologic difference between the two was dependent solely upon the presence of cellular infiltrations in the latter instance, many who observed these cases felt that they might be variations in degree of abnormal hematopoietic system response to infection and not two different biologic processes.

Considerable speculation followed examination of the microscopic sections in Case 8. The diagnosis of leukemia could not be made, although it was obvious that there had been a profound alteration in the hematopoietic system. The possibility arises that had the infection been slightly less acute and had he lived a few days longer, the microscopic lesions of acute leukemia might have had a chance to develop.

The last 2 cases present a very close relationship between the existing infection and the abnormal blood picture. In both of these cases the diagnosis of leukemia was made before death and confirmed at autopsy. It seems fairly clear that the infection in these 2 instances antedated the leukemic changes in the blood. It is possible, therefore, that the blood picture and the cellular infiltration into the various tissues, both quite typical of leukemia, represent a very unusual response on the part of the hematopoietic system to massive infection. Although it is, of course, possible that there was a simultaneous occurrence of these two conditions, the clinical course and autopsy findings strongly suggest that the white blood cell changes were dependent upon the infection. In both these instances, the requirements of the diagnosis of leukemia are satisfied and it seemed probable that the infection was of considerable importance as an etiologic factor in the alteration of the blood.

The preceding group of cases represent a reaction on the part of the bone marrow to stimulation with an overproduction of young and abnormal white cells.

**Depression of Leukopoiesis.** The following records are presented as instances of depression of the white blood cell elements rather than stimulation. Depression of the white blood cells is known as leukopenia. Leukopenia is the accepted response in such diseases as typhoid fever, chronic tuberculosis and malaria. Leukopenia during the course of disease, usually associated with leukocytosis, has been observed and its frequently serious prognostic significance appreciated.

For extreme degrees of depression of the granular leukocytes the term agranulocytosis has been employed. This has been observed in association with a variety of conditions. A number of cases have now been collected reporting the occurrence of agranulocytosis following intravenous use of arsphenamin.<sup>1</sup> Several instances of this leukocytic reaction to sepsis have been seen,<sup>2</sup> and this type of blood picture in association with an acute necrotizing infection of the throat has been sufficiently observed and recorded to have become the well-established entity of agranulocytic angina.

As an example of agranulocytic angina the following case abstract is presented:

CASE 13.—J. F., Unit 244547. An unmarried American woman, aged 55 years, who had been in relatively good health prior to the onset of the present illness. One week before admission she was suddenly seized with



an acute sore throat associated with fever, chills and extreme prostration. At the time of admission she was stuporous and desperately ill. Temperature, 104° F.; pulse, 120; respirations normal. The physical examination was essentially negative except for a widespread redness of the gums and pharynx. The tonsils were buried and covered with a grayish sloughing membrane. The cervical lymph nodes were very slightly enlarged and not tender. On admission her blood count showed red blood cells, 4,100,000; hemoglobin, 80 per cent. The white cells numbered 1400, no polymorphonuclears being seen. Smears from the gums and from the sloughing membrane were unsatisfactory, showing a variety of miscellaneous organisms with probably a few Vincent's organisms. Culture of the gums and throat revealed both hemolytic and nonhemolytic streptococci, *Staphylococcus albus*, as well as other organisms. No *Bacillus pyocyaneus* was observed. Blood cultures remained sterile throughout the course of the illness. In spite of daily transfusions during the 14 days she was in the hospital her daily white blood count never rose above 2000 and only 3 polymorphonuclear leukocytes were observed during this entire time. She died 3 weeks after the onset of the symptoms. At no time was there any evidence of jaundice. At autopsy, a necrotizing, sloughing lesion was found involving the membranes of the mouth, pharynx, larynx and upper trachea. There was a terminal bronchopneumonia. The bone marrow was semifluid and reddish in color. The red blood cell elements appeared to be normally distributed. There was almost complete absence of granulocytes and their precursors. There were no other changes of note.

The same general type of syndrome has been seen here, and has been observed elsewhere, following operative procedures upon the teeth or tonsils.

The following case is an example where this reaction was apparently intimately associated with removal of the tonsils:

CASE 14.—C. B., Unit 73733. A Swedish housewife, aged 47 years, 1 week before admission, had her tonsils removed. The day following tonsillectomy she developed a severe sore throat and a temperature which ranged between 103° and 105° F. until the time of admission. Examination revealed a desperately sick, middle-aged woman with swollen tongue. The pharynx was edematous and covered with a grayish necrotic slough. Her temperature was 105°, rising to 106° F. 5 days later when she died. There was a mild secondary anemia. White blood cells on 4 separate examinations ranged between 400 and 800 per c.mm. At no time were any polymorphonuclears observed. The blood Wassermann was negative. The blood culture remained sterile. At autopsy a necrotizing infection of the pharynx and trachea was found with complete suppression of all cells of the granulocytic series in the bone marrow, as well as in the blood. A great variety of organisms occurred in the slough, including Vincent's organisms, spirochetes, and some of the leptothrix group.

In addition to the group of cases that conform in all respects to the accepted description of agranulocytic angina, a large number of interesting variations have been observed. Similar cases have, in most instances, been previously reported in the literature. There have been several reports to date of this type of response in individuals receiving antitubercular treatment (1) and one instance of this has been observed here. In addition, this type of bone marrow depression has been observed with several different types of infec-

tious diseases. These include cases of localized infection as well as general septicemia. Although the *Bacillus pyocyaneus* was at one time thought to be a possible factor in this white cell depression, subsequent case analyses have shown that this organism is rarely present. One case has been observed in the wards of this hospital in which this organism was apparently the etiologic agent. In this instance the lesion was localized and superficial, in a location that permitted prompt local therapy, with a resulting disappearance of the lesion and a return of the blood picture to normal.

CASE 15.—S. W., Unit 825352. A graduate nurse, married, aged 45 years, with irrelevant past history who, 5 days before admission, developed sore throat and fever. At the same time she noticed a sharp pain in the rectum. The throat continued sore and the pain in the rectum increased. The temperature on admission was 104.8° F. Examination revealed an acutely ill, middle-aged woman. Her tonsils were large and boggy with occasional spots of whitish exudate. Her throat was only moderately inflamed and no ulcers were observed. Near the anal orifice on the left side were 2 shallow ulcerations covered by a grayish slough. Culture of the throat revealed a variety of organisms. Culture of the anal ulcers grew out almost pure *Bacillus pyocyaneus*. On admission the red count was normal, white blood cells were 1700; polymorphonuclears, 16 per cent; lymphocytes, 75 per cent. It was felt that the relative agranulocytosis was probably related to the anal ulcers and not to the mild pharyngitis. Treatment of the anal ulcers with Lugol's solution and dilute tincture of iodine resulted in prompt healing, with return of temperature to normal on the third day and rapid increase in the polymorphonuclears, the total white cells reaching 2400 with 48 per cent polymorphonuclears at the end of the first week, and 7500 white cells with 70 per cent polymorphonuclears at the end of the second week at which time she was discharged. Blood cultures on admission remained sterile. She has subsequently returned to work without symptoms of any kind.

The agranulocytic type of blood picture has been observed in association with a rapidly spreading staphylococcus carbuncle of the face.

CASE 16.—F. F., Unit 79835. A man, aged 76 years, came in complaining of an infection on the right cheek of 4 days' duration. On admission his temperature was 101.2° F., pulse 102. The mouth and throat were normal. On the right cheek was a small indurated furuncle. Red blood cells, 4,000,000; hemoglobin, 80 per cent; white blood cells, 1300; polymorphonuclears, 0; lymphocytes, 94 per cent; monocytes, 6 per cent. In spite of treatment of the furuncle on the cheek and several transfusions, the infection spread rapidly, involving half of the face and neck, with beginning gangrene. His temperature rose to 104° F. on the fourth day, and he died on the sixth day. At no time, even immediately after transfusions, were any polymorphonuclears seen in the blood. Blood cultures were sterile. Cultures from the cheek grew out a pure culture of hemolytic staphylococcus aureus.

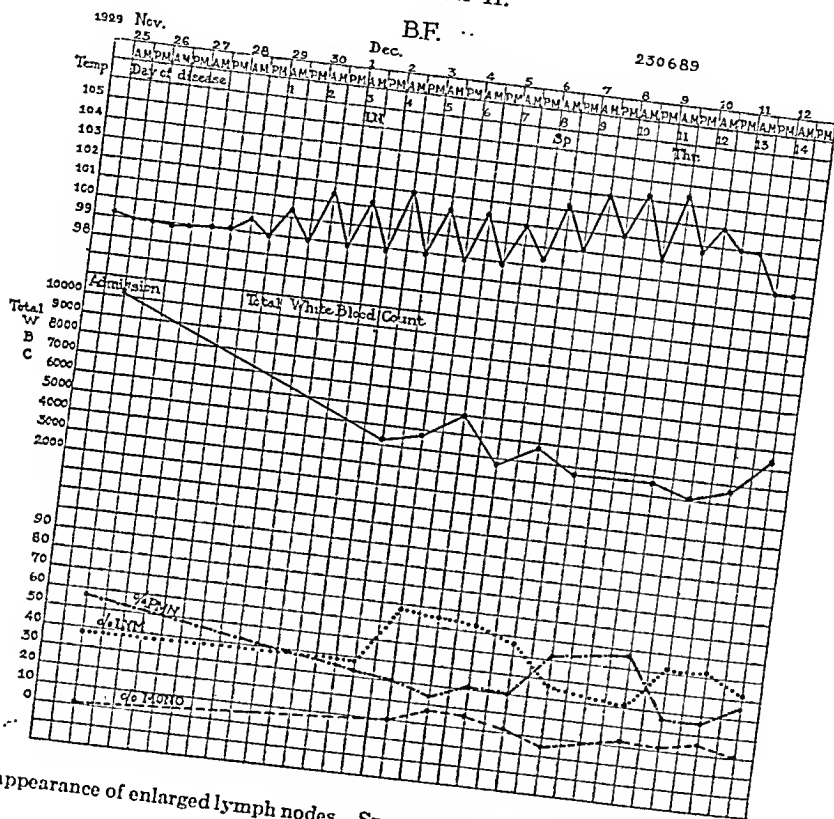
A group of 7 cases that presented strikingly similar clinical pictures have been observed here during the past year. These have been collected and published as examples of extreme depression in the granulocytic cells of the blood in association with a transient,

# 348 THOMPSON: ABNORMALITIES IN WHITE BLOOD CELL RESPONSE

relatively mild pharyngitis.<sup>3</sup> It is of interest that all the cases of this group, with but one possible exception, recovered promptly with return of the blood picture to normal. A typical example of this group is presented here.

CASE 17.—B. F., Unit 230689. A Jewish subway guard, aged 40 years, was admitted to the medical wards for study of a mild hyperthyroidism. His admission blood count showed 4,700,000 red blood cells, 10,300 white blood cells; 56 per cent polymorphonuclears; 37 per cent lymphocytes, 7 per cent monocytes; no abnormal cells were seen. For the first 3 days his

CHART II.



LN, appearance of enlarged lymph nodes. Sp, appearance of spleen; Thr., appearance of pharyngitis.

temperature remained normal. On the 4th day it began to be progressively elevated. For the next 2 weeks the temperature was spiking in character, being normal in the morning, rising in the evening to between 102° to 103°, reaching 104.2° F. at one time. There were no symptoms with the initial rise in temperature and no physical signs to explain it other than a very slightly reddened throat. After a week of this unexplained fever moderate enlargement of the posterior cervical lymph nodes was noted. On the 4th day of this acute illness the red blood count was found to be normal, the white blood cells had fallen to 4000; 33 per cent polymor-

phonuclears. Frequent white blood counts during the next 10 days are shown in the accompanying chart. (Chart II.) On the 10th day of this acute illness the patient was still without symptoms and there was no change in the appearance of the throat. The glands were thought to be larger and were described as soft and slightly tender. The tip of the spleen could just be felt on deep inspiration. It was not until the 12th day that his throat was noticed as being more diffusely reddened than previously, and on the day following, small, white, round, superficial ulcerations, resembling *Staphylococcus albus* colonies on a blood plate, were seen. With the appearance of these, the temperature began falling, reaching normal on the 16th day. This was followed by rapid clearing of the throat lesions, prompt regression of the lymph nodes, and a rapid return of the blood count to normal.

The agranulocytic type of blood picture has also been observed in association with descending infection of the respiratory tract with terminal pneumonia and empyema.

CASE 18.—J. S., Unit 70607. A young boy, aged 19 years, came in with a history of a severe sore throat beginning 1 week before admission. The day following the onset of the sore throat, a peritonsillar abscess was incised with transient relief of the pain. Three days before admission he became much worse, with high fever, pain in the chest, and a cough productive of blood-tinged sputum. Temperature, 105° F.; pulse, 132; respirations, 38. Examination revealed a desperately sick young man. There was a sloughing area on the anterior part of the right tonsil and the physical signs of consolidation of the left lower lobe. The next morning the physical signs changed somewhat and fluid was suspected. Thoracentesis revealed 800 cc. of thin, yellow, foul-smelling fluid which contained a mass of organisms from which hemolytic streptococcus, pneumococcus IV, and various anaërobcs were recovered. He became rapidly worse and died 24 hours after admission.

His red blood count was 4,000,000; hemoglobin, 75 per cent; white blood cells, 100; polymorphonuclears, 3 per cent. There were 58 per cent of typical small lymphocytes and 39 per cent large immature cells thought to be myeloblasts.

It seems probable that this case originally represented a peritonsillar abscess. Following incision gangrene of the lung developed with subsequent empyema. The blood picture showed marked depression in the number of mature polymorphonuclears with a very high percentage of immature granulocytes. Some felt that this blood picture represented an acute leukemia, but most of those who saw the patient and the blood smears thought that the leukocytic picture represented a severe agranulocytic type of reaction to an overwhelming infection with an attempt on the part of the bone marrow to put out cells. Autopsy was not obtained.

Another variation that has been observed is illustrated in the following cases of hemolytic streptococcus infection with terminal hemolytic streptococcus septicemia:

CASE 19.—I. R., Unit 84664. An American graduate nurse, aged 37 years, who had a sore throat and tonsillitis during the 10 days before admission. During the 2 days before she came in, her temperature rose

rapidly, reaching 104° F., and there was marked prostration. On admission she had a temperature of 106°, pulse 130, and she was obviously *in extremis*. Over the entire body there was a diffuse erythematous rash which faded on pressure. Her tonsils were deep red, swollen, and each was covered with a whitish-gray slough. The examination was otherwise negative. The red count was normal; white blood cells, 150; polymorphonuclear, 0. The blood culture grew out a heavy growth of hemolytic streptococcus. Her temperature rose rapidly to 108° and she died.

Autopsy revealed a fulminant throat infection with invasion of the blood stream by hemolytic streptococcus. No metastatic foci were found. The bone marrow was deep red and contained abundant mature and immature red blood cells, but almost no cells of the granulocytic series.

CASE 20.—A. R., Unit 266942. An elderly Irish housewife came into the surgical ward complaining of having burnt the fingers of one hand 48 hours previously. During the preceding 2 months she had felt slightly tired but was otherwise quite well. The original burn was not particularly severe but had been followed by rapidly progressive inflammation of the dorsum of the hand. On entrance she was acutely ill with a temperature of 104° F. and there was an acute, rapidly spreading cellulitis of the hand and an associated lymphangitis and lymphadenitis. There were no petechiæ. Admission blood count showed a normal number of red cells but only 480 white blood cells with no polymorphonuclears. The local infection spread rapidly. Hemolytic streptococcus was recovered from it and from the blood, and the patient died 3 days after admission. On the day before death her white cells numbered 520 and there were still no polymorphonuclears.

CASE 21.—B. M., Unit 70314. An American, aged 65 years, came in complaining of frequency and nocturia for 2 years with complete anuria for 10 hours. On admission he was found to have an enlarged prostate. A suprapubic prostatectomy was done in two stages and except for rather violent postoperative rises in temperature, his convalescence following the second operation seemed entirely satisfactory. His blood count during this entire time was normal, except during the febrile reaction to the first operation, when the total white cells numbered 31,000; 85 per cent polymorphonuclears. Two weeks after the second operation the white blood cells were 7200, polymorphonuclears, 82 per cent. After several days of normal temperature and with beginning closure of the abdominal wound, he was allowed in a chair for several days, but developed, a week later, what was apparently a mild bronchitis. This promptly cleared and again convalescence was satisfactory. Then he developed an acutely sore throat with a rapid rise in temperature to 105° F. White blood cells on this day were 3800; polymorphonuclear, 0; 95 per cent lymphocytes, 5 per cent monocytes. He became rapidly worse, his temperature rose to 106° F., and 3 days after the onset of symptoms he died. Blood cultures grew out hemolytic streptococcus in both flasks. Cultures of the throat, which was infected and acutely inflamed, revealed a large number of hemolytic streptococci. Autopsy was not obtained.

This case was of particular interest in that the entire terminal illness occurred while the patient was under observation in the ward. Previous blood counts had been done. In these a normal response to infection had been observed. While under observation and while convalescing satisfactorily from the prostatectomy he was infected with unusually virulent hemolytic streptococcus. This

infection was rapidly progressive and was associated with an extreme depression of the leukocytes.

**Discussion.** In the last group of unusual white blood cell pictures there has been a selective depression of the granular elements. This blood picture conforms to the accepted definition of agranulocytosis. In all of these cases infection has existed. Apparently coincident with this infection there has been a deviation of the blood picture from the normal.

The question of the etiologic importance of the infection in the production of this blood picture has not been settled. Some observers believe that the infection, present in nearly all of these cases of agranulocytosis, is secondary to a primary bone marrow depression of unknown etiology. Clinical reports are cited to substantiate their views. One of the most recent and best studied is the case presented by Roberts and Kracke.<sup>4</sup> Other authors think that agranulocytosis is a peculiarly selective type of bone marrow response to a wide variety of toxic agents.<sup>5</sup> It is still an open question and one that will probably not be definitely settled until enough accurate clinical data have been obtained and analyzed, or until such time as a similar syndrome may be studied in the laboratory.

Observation of our cases has been of little assistance in settling this question. In our opinion, however, several of these cases offer clinical evidence in support of the impression that the infection was of primary importance in the production of this syndrome. In this connection, Case 15 was of particular interest in that the patient's infection was in a location and of a type that permitted immediate local treatment. With the regression of the infection there was a prompt return of the blood picture to normal and progressive improvement in the patient's general condition. In Case 21 previous blood counts had shown a normal response, but with the advent of the new and virulent hemolytic streptococcus infection, the agranulocytic type of blood picture developed.

We realize, in this group, as in the previous group, the futility of drawing definite conclusions from the observation of limited clinical material. We believe, however, that these patients as we have seen them strongly suggest that the presence of a toxic agent within the body, whether this be a relatively simple chemical such as neoarsphenamin or the complicated products of an infection, may be of considerable importance in the production of this selective bone marrow depression.

**Conclusion.** Two groups of cases are presented in which there has been an unusual white blood cell picture. In the first group, stimulation of the leukocytic elements produced various strange blood pictures, several of which were indistinguishable from leukemia. In the second group depression of the granular cells resulted in agranulocytosis. In all these cases infection existed. The pos-

sible relation between the presence of the infection in the body and the coincident deviation of the blood picture from the normal is discussed.

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### PNEUMOPERITONEUM IN THE TREATMENT OF TUBERCULOUS ENTEROCOLITIS.

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TUBERCULOUS disease of the intestines is far more frequently a complication of pulmonary tuberculosis than is generally realized. Schwatt and Steinbach<sup>1</sup> estimate that tuberculous ulcers of the intestines occur in from 60 to 90 per cent of cases of fatal phthisis. Walsh<sup>2</sup> found 76 per cent and Engelsmann<sup>3</sup> 92.6 per cent intestinal ulcerations in patients dead of pulmonary tuberculosis. It is evident from these data that the majority of our far-advanced pulmonary cases acquire this condition some time during the course of the disease. Still it is generally admitted that no such high percentage of patients with far-advanced pulmonary tuberculosis is treated for intestinal tuberculosis. Steinbach<sup>1</sup> reports that of 127 cases of intestinal tuberculosis, in which definite ulceration was found at necropsy, no diagnosis in 78 (61.5 per cent) was arrived at during life because of the absence of clinical symptoms referable to the intestinal tract. It may be reasonably presumed that a similar state of affairs prevails in all tuberculosis institutions throughout the country. Searching for reasons why no adequate attention is given to this most frequent complication of pulmonary tuberculosis, the following points seem to be obvious: (1) Lack of diagnostic consciousness; (2) improper interpretation of symptoms and signs; (3) incomplete diagnostic investigation; (4) asymptomatic forms of intestinal tuberculosis.

Stewart<sup>4</sup> aptly says that if we are not aware of serious trouble until the well-known late and grave symptoms of intestinal tuber-

culosis, such as diarrhea with foul-smelling stools, emaciation, tenderness, pain and sudden collapse, develop, we are just where our grandfathers were with consumption half a century ago.

**Onset and Symptoms.** The onset of tuberculous enterocolitis simultaneously with the pulmonary process is comparatively rare. In the overwhelming majority of cases the onset follows several months or years of observation of the pulmonary disease. It must be kept in mind that macroscopic ulceration, hyperplasia or cicatricial stenosis are later changes in the course of tuberculosis of the intestines. These changes are preceded by stages from a solitary tubercle localized in the mucosa, or the lymphatic tissue of the submucosa, to conglomeration of tubercles and microscopic ulcerations. Furthermore, such conglomerate tubercles distributed in different portions of the intestinal tract may persist without ulceration for a long time. There is no parallelism between the extent of intestinal involvement and the intensity of symptoms. Minor pathologic changes limited to a small portion of the intestine may cause severe symptoms and *vice versa*. Symptoms such as anorexia, aversion for food, fullness after eating a small amount of food, distress after eating, sour stomach, heart burn, eructation, nausea, constipation, abdominal pains aggravated by eating and relieved by fasting, may be observed during the early developmental stages of the disease. At the same time, it is noted that the patient is not doing well, though the pulmonary condition seems to be stationary or improving. Rise in temperature, malaise, failure to gain or rapid loss of weight otherwise unexplained and nervous irritability often accompany the onset.

It was suggested by Paterson<sup>5</sup> that starvation for 48 hours caused the disappearance of symptoms, particularly the fever; in these cases this is used to determine whether the symptoms have their origin in the lungs or in the gastrointestinal tract. Diarrhea is not characteristic of ulceration in the large intestine. It may be present in cases of ulceration in the large or the small intestine or both. It is usually indicative of extensive involvement. Constipation should not be taken as a sign of ulcer formation in the small intestine, nor constipation alternating with diarrhea as indicating ulceration in the small and the large bowel. Pain on deep palpation is suggestive of ulceration, but the point of maximum tenderness does not necessarily coincide with the site of maximum involvement. Rigidity of the abdominal wall is indicative of disease of the serosa.

The absorption of tuberculotoxins from active pulmonary foci undoubtedly may cause diminished hydrochloric acid secretion in the stomach with functional impairment in other parts of the gastrointestinal tract, resulting in anorexia, epigastric distress, eructation, nausea, vomiting, gas distress, flatulence, colic, irregular bowel action, loss of weight and increased nervous irritability. If such symptoms persist or become worse in spite of adequate treat-



ment of the pulmonary process, a diagnostic survey of the case for intestinal tuberculosis should be urged. It is safer to be overzealous in the detection of early intestinal tuberculosis than to discover it too late. The deficit in the defense of the body due to intestinal tuberculosis should be recognized and eliminated at the earliest possible time. Naturally, nontuberculous diseases of the gastrointestinal tract, such as peptic ulcer, nonspecific enterocolitis, malignancy, amyloidosis and digestive disturbances due to dietetic errors, must be differentiated.

**Diagnosis.** It is possible to establish the diagnosis of intestinal tuberculosis on the basis of symptoms and physical findings. Still it seems advisable that corroborative evidence be obtained by means of Roentgen ray in all cases, with manifest as well as suspected intestinal lesions. Smithies, Weisman and Fremmel<sup>6</sup> are of the opinion that "no person in whom pulmonary tuberculosis is proved or suspected can be considered as having been properly examined without a roentgenologic study of the alimentary tract." A positive Stierlin sign, that is, failure of the barium meal to remain in the cecum and ascending colon 6 or 7 hours after ingestion of the progress meal, while the terminal ileum and the transverse colon are filled, indicates infiltrative or ulcerative tuberculosis of the cecum or the ascending colon. This phenomenon is due to increased irritability and hypermotility of the involved areas. Nontuberculous inflammatory conditions causing an absence of the normal shadow are rarely localized within 12 inches proximally or distally to the ileocecal valve. A negative Stierlin sign does not exclude tuberculosis of the cecum or ascending colon. A localized or generalized hyperperistalsis resulting in "filling defects" may be present in very early as well as in very extensive lesions. Hypertrophic circular scars may cause easily demonstrable partial obstruction. Brown and Sampson<sup>7</sup> point out, that if the site of the ulceration is in the small intestine, as a result of hyperirritability and spasm, a temporary stasis and dilatation of the proximal segment develop. Barium meal should never be omitted whenever the question of a possible intestinal tuberculosis arises. Deformities due to adhesions, or malignancy of abdominal organs, syphilis and nontuberculous inflammatory disease of the intestines must be excluded.

Laboratory methods afford little aid in diagnosis, with the exception of positive findings as to blood in the stools that is suggestive of intestinal ulceration. Erickson<sup>8</sup> reports intestinal bleeding in 13 per cent of his cases, in 6 per cent of which there was a real hemorrhage.

Even using utmost care in evaluating clinical, roentgenologic and laboratory data, it may be impossible to arrive at a correct diagnosis. (1) Because our present-day methods have their limitations, as emphasized by Steinbach,<sup>9</sup> stating that in 52 per cent of his 67 cases of far-advanced pulmonary tuberculosis, in whom a com-

parative study of the clinical and postmortem findings was made, the roentgenologic signs considered diagnostic of intestinal tuberculosis were highly unreliable. (2) Because there are cases of this complication without pain or any other subjective manifestation, cases that are never recognized as such unless on the postmortem table.

The prognosis of intestinal tuberculosis is not necessarily hopeless, even if it is accompanied by far-advanced pulmonary tuberculosis. Complete healing of exudative and ulcerative lesions was observed in animal experiments, roentgenologically, clinically and on the postmortem table. We think that with the available diagnostic and therapeutic facilities a therapeutic pessimism or negativism is not more justified than the omission of adequate sanatorium treatment in pulmonary forms.

**Treatment.** If the plea of the phthisiologist for early diagnosis of pulmonary tuberculosis is reasonable and justified by the far higher percentage of recoveries in early than in advanced cases, it is only logical to extend a similar plea to the phthisiologist concerning intestinal tuberculosis. The cure of any form of tuberculosis lies in its early diagnosis. The attitude of Stewart<sup>4</sup> deserves wide attention and propagation. He says: "In some cases when symptoms begin lesions have already become gross. To wait for symptoms is to wait months beyond a time when a diagnosis can be made by the barium meal. The only proper method is to anticipate symptoms, discover the disease before it is gross enough to show them, and make the diagnosis without them." Besides protection of the abdomen and decrease of exercise, if necessary to absolute bed rest, the following methods are available for the treatment of intestinal tuberculosis: (1) Prophylactic, (2) dietetic, (3) medicinal, (4) ultraviolet and Roentgen ray irradiation, (5) surgical and (6) pneumoperitoneum.

Kantor<sup>10</sup> emphasizes the importance of prophylaxis in the treatment of secondary intestinal tuberculosis. He offers four measures for this purpose: (1) The avoidance of swallowing tuberculous sputum. The finding of tubercle bacilli in 90 per cent of the stools of patients with open tuberculosis of the lungs highly justifies this standpoint. (2) Administration of dilute hydrochloric acid in the subacidity cases. This latter suggestion is supported by the investigations of Rolleston<sup>11</sup> that show that ulcers extend higher up in the intestinal tract of patients suffering with anacidity than in cases with normal acidity. (3) The prevention of intestinal stasis and the eradication of all forms of constipation. Any factor that would prolong the sojourn of fecal material in the terminal ileum and cecocolon, which is normally about 3 to 5 and 18 to 33 hours respectively, must be eliminated. The prevention of fecal retention will decrease the opportunity for tuberculous infection. (4) Prompt and comprehensive survey of every tuberculous dyspeptic.

It is erroneous to force amounts of food overstepping the patient's tolerance in gastrointestinal subcompetency due to tuberculosis. Food given over tolerance will not be utilized and will cause harmful irritation. The optimum diet is the minimum maintenance diet based on basal caloric requirements. Kantor<sup>10</sup> recommends for routine feeding the Schmidt intestinal test diet containing proteins, carbohydrates and fats in well-balanced ratio. Meals must be small in bulk, cellulose-free, of smooth consistency, thoroughly strained, composed of easily assimilable foods not causing fermentation. When diarrhea is pronounced liquid diet is indicated. By bland diet irritation of the inflamed surface and ulcerated areas is avoided, and thus cramping pain and diarrhea may be alleviated. Milk should be used cautiously and preferably in small quantities, because its undigested curds may irritate the bowels and cause diarrhea. It may be said, that in general, dietetic treatment alone is not an adequate therapeutic procedure. During more than a year of experience with the Sauerbruch, Hermannsdorfer, Gerson diet we found that patients with gross intestinal tuberculosis tolerate the "salt-free" diet very poorly.

In case of diarrhea intravenous injection or oral administration of calcium, oral medication with bismuth, tannic acid, atropin and opium preparations may be given. In some cases bowel irrigations with physiologic saline solution or with appropriate solutions of astringents and antiseptics as tannic acid, silver nitrate and mercurochrome may give relief.

Excellent results were observed by several investigators after treatment with natural and artificial sunlight. Brown and Sampson<sup>7</sup> report that of the group treated by ultraviolet irradiation 65 per cent improved and 40 per cent were free of symptoms after treatment for 1 month; after 2 months' treatment 70 per cent were improved and 60 per cent became symptom-free, all patients were improved and 85 per cent had lost all symptoms after 6 months' treatment. Bacmeister<sup>13</sup> saw favorable effects upon intestinal tuberculosis from the use of Roentgen ray irradiation.

Valuable information as to the surgical management of intestinal tuberculosis was brought out by Smithies, Weisman and Fremmel.<sup>6</sup> They state that no surgical operation should be performed in patients with rapidly progressing toxic pulmonary lesions complicated by extensive intestinal involvement without any reparative tendency. The physical and Roentgen ray findings of the abdomen are marked, and ischiorectal abscess and exudative peritonitis are frequent complications in these cases. Early exploratory laparotomy and removal of the diseased portion of the intestine under local or spinal anesthesia is recommended by them in two groups of patients: (1) In mildly active or quiescent pulmonary tuberculosis accompanied by dyspeptic disturbances of rather mild and irritative character; also constitutional symptoms are absent, as well as

evidence of gross anomalies on abdominal examination; (2) in patients with quiescent or intermittently active, extensive pulmonary processes, in which intestinal tuberculosis develops in the later course of the thoracic disease. There is usually definite pain, diarrhea, malnutrition, dehydration, prostration; the physical and Roentgen ray findings indicate well-localized lesion of mild degree in the terminal ileum, cecum or the colon. Archibald<sup>12</sup> reports also favorably on the surgical treatment of intestinal tuberculosis.

**TREATMENT BY PNEUMOPERITONEUM.** Pneumoperitoneum with oxygen was given in 44 of our cases. The inflations were done between breakfast and lunch, preferably not too close to the noon hour, to avoid possible interference with the patient's meal. No special preparation is necessary except the evacuation of the bladder just before operation. Enemas or cathartics are not used, (1) because of the discomfort and weakness, and (2) because there is no accumulation of fecal material in the irritated hyperperistaltic intestines. In patients with severe cough an adequate dose of codein is given 1 hour before treatment. The best site for injection is three fingers' breadth below and to the left of the umbilicus, although in cases where the left side is used too often fibrosis and adhesions develop, preventing the smooth introduction of the needle, the same level can be taken on the right side. Injury to the deep epigastric artery, mesenteric vessels and intestines causing embolism, hemorrhage, peritonitis, furthermore the danger of peritoneal shock, are so remote that they do not militate the least against the use of this procedure. No occurrence of subcutaneous emphysema or collapse due to sudden absorption of the injected oxygen was seen in this series.

One per cent novocain is used for infiltration of the abdominal wall, particular attention being given to the peritoneum to avoid shock. By elevating a skin fold between thumb and index finger a small skin incision is made to aid smooth insertion of the Floyd-Robinson needle. The size and shape of this needle facilitates introduction into the abdominal cavity as well as the inflation of oxygen from a standard pneumothorax apparatus. The direction of the needle should be diagonal, pointing upward and toward the midline, to ensure perfect closure and prevent the back flow of oxygen under increased abdominal pressure. Only exceptionally do we find patients with heavy abdominal walls, that necessitate a perpendicular perforation, because the diagonally inserted needle would not reach the peritoneal cavity. Manometer readings are taken following insertion of the needle, though it is well known that the manometer does not have such important and indispensable rôle in pneumoperitoneum as in artificial pneumothorax treatment. The intraädominal pressure is neutral in untreated cases. Since there is not any initial intraädominal negative pressure, the operator must get his orientation from lack of resistance when the

needle enters the peritoneal cavity. Slight positive pressure, amounting to from 0.5 to 1 cm. of water, was very rarely seen in patients without previous treatment. It can be said that the manometer is not as sensitive an indicator of the air content of the abdominal as of the pleural cavity. Positive pressure and oscillations appear usually after the inflation of 300 to 500 cc. of oxygen. Still in some instances the oscillations as well as the appearance of positive pressure are not evident even after 1000 cc. of oxygen were injected. In such cases the disappearance of liver dullness after the injection of 300 to 400 cc. of oxygen or the subjective feeling of the patient will serve as useful guides as to the presence of air in the peritoneal cavity. The right hypochondriac area can be easily percussed by "palm" percussion by the operator himself. This method may often give us early information of a correctly performed inflation before any sensation is indicated by the patient. A tympanitic percussion note over this area following injection of more than 500 cc. of oxygen is absent only in cases where the space between the liver and the overlying abdominal wall is obliterated by adhesions, as we had the opportunity to observe in some of our cases. Two other interesting phenomena were recorded: (1) That in some instances positive pressure (+3 and +4) following the injection of from 750 to 1200 cc. of oxygen disappeared after few respirations, though the absence of liver dullness, distention and loud tympanitic percussion sound of the abdomen and subjective feeling of the patient indicated the presence of oxygen; (2) in 3 patients a paradoxical oscillation in the manometer, that is, a decrease of the pressure by about 1 cm. of water on deep inspiration and a return to its original level on expiration was seen after the inflation of considerable amounts (800 to 1000 cc.) of oxygen. Normally the positive pressure is increased on inspiration and decreased on expiration. The flow of oxygen is slower than one is used to seeing in giving artificial pneumothorax, due to the absence of the suction effect of negative pressure. To increase the speed of flow it is advisable to elevate the second bottle (containing water).

An early sharp rise of positive pressure with too wide oscillations should be considered a sign of adhesions. No unduly large amounts of oxygen should be forced into the abdominal cavity, in such instances, to avoid undue tension and discomfort. The subjective feeling of the patient, the distention of the abdomen and increased intensity of tympanitic percussion sound are far better guides in controlling the amount of oxygen injected than the manometer. Great variations in the sensory reaction to the inflations were met with in different patients. The sensibility of the patient, the size of the abdominal cavity, presence of tuberculous peritonitis and adhesions, limitation in motion of the diaphragm and the extent of the pulmonary disease are the main factors in this respect. The

extent of the intestinal involvement in itself has no great significance, if any, in this connection. Patients with extensive involvement were given large amounts of oxygen without discomfort, while several cases with less extensive disease had marked complaints due to distention following the inflation of comparatively small amounts of oxygen. In some patients with severe bilateral pulmonary tuberculosis the sudden rise of the diaphragm induced by the injected oxygen caused considerable dyspnea. There is usually no indication of fullness or pain at the level of the diaphragm or in one of the shoulders when less than 300 cc. of oxygen are given. Indication of such sensations is more frequent after 500 cc. In all but 2 instances diaphragmatic or shoulder pain were indicated when more than 1000 cc. was introduced. Where tension and discomfort were minimal the patient was allowed to walk back to his room, and his prescribed daily routine was not changed because of the pneumoperitoncum. Still in the majority of cases it was necessary to relieve the discomfort due to tension or shoulder pains by elevating the foot of the bed. This simple measure by shifting the oxygen from below the diaphragm toward the pelvis, a change not unlike the shifting of the air bubble in the carpenter's level, proved to be successful in practically all cases where it was used. In 24 to 48 hours these patients resumed a normal position without being conscious of any abdominal distress due to treatment. This can be explained by the fact that there is a rapid absorption of the injected oxygen, with a complete disappearance of it in a few days. We had the opportunity to observe that in some patients the absorption rate diminished with the increasing number of inflations.

The amount of oxygen should be adapted to the requirements of the individual case, the chief criterion being the subjective response of the patient during operation. The abdomen should be rather under than overinflated because pressure or tension may become more noticeable to and discomforting for the patient when he leaves the operating table or tries to occupy a semirecumbent position in his bed. The largest amount of oxygen injected was 1500 and the smallest amount 150 cc. Often the amount of oxygen was gradually increased until about 1000 cc. was reached, and then the patient was carried on such doses as long as it was deemed necessary. It was noted that patients required inflations at certain intervals, the length of which varied from 1 to 2 weeks, rarely longer, and only in 1 instance as short as 3 days. In Cases 20, 31, 35 and 36 the inflation tolerance, that is, the intraabdominal capacity, markedly decreased as the course of treatment progressed. In Case 20 the oxygen was reduced from 1000 to 500, in Case 31 from 1000 to 300, in Case 35 from 1000 to 600 and in Case 36 from 1000 to 150 cc. This decreased intraabdominal capacity is undoubtedly due to developing adhesions.

Complaint of nausea, following and apparently caused by the

inflation, was met with only once. In 1 of our cases in whom the oxygen injection was given during menstruation severe cramping pains developed in the lower part of the abdomen; in a patient having taken several inflations the injection of 950 cc. of oxygen was followed by a feeling of tightness in the heart region, at the same time the abdomen appeared dilated and the position of the diaphragm was found to be high. In Case 20, at the thirteenth inflation, the amount of oxygen having been reduced from 1000 to 500 cc., when the patient returned to her room she felt "something snap" below the ribs on the right side, had excruciating pains at the level of the diaphragm that did not improve on elevating the foot of the bed and gradually disappeared in 3 days. It may be reasonably supposed that the reflex nausea, irritation of the female genital organs in menstrual congestion, undue upward displacement of the diaphragm with cardiac embarrassment and stretching or separation of the adhesions were caused by unduly high intraabdominal pressure. Such disagreeable incidents can be prevented by avoiding the menstrual period and not forcing too large amounts of oxygen into the abdominal cavity.

Expectoration, with or without increased cough, may be increased during the first 2 days following inflation. This is due to the elevation of the diaphragm that can be visualized under the fluoroscope or on the roentgenogram. If abdominal tightness or shoulder pains are present the cough is usually decreased, since the patient is automatically trying to avoid discomfort resulting from cough.

It is conceivable that the elevation of the diaphragm may exert a favorable influence upon the healing of the pulmonary process by limiting the excursions of the diaphragm and by decreasing the intrapleural negative pressure, which, in turn, will increase the blood supply of the pulmonary tissue. Still it is known that the injected oxygen is absorbed in 2 to 3 days. Therefore, an indirect curative effect upon the pulmonary process may be discounted or considered irrelevant in face of the fact that inflations are repeated at 1 or 2 weeks or longer intervals, and thus the high level of the diaphragm is maintained only during a small fraction of the treatment.

The greatest upward displacement of the diaphragm was observed in Cases 33 and 37. In the first, pneumoperitoneum was instituted following a block of the right phrenic nerve, and in the second case, after bilateral phrenic paralysis was surgically established. It is remarkable how well and easily this latter patient adapted herself to the changed respiratory mechanism of her body. Another unusually interesting patient was Case 36, who was treated simultaneously by bilateral artificial pneumothorax and pneumoperitoneum, taking 400 cc. of air on each side of the chest and 500 to 1000 cc. of oxygen intraperitoneally without manifest discomfort or respiratory embarrassment.

The mechanism of the effect of injected oxygen upon the intestinal

lesions is not exactly known. Of the different hypotheses two seem to be most compatible with the results obtained: (1) Oxygen increases cell activity in all body tissues, effecting a better local and general immunologic response; (2) injected oxygen due to its chemical properties and increased intraabdominal pressure will cause irritation of the peritoneum and intestinal serosa with subsequent hyperemia. A decrease in the peristalsis following oxygen inflations was noted in the majority of our cases. By these accomplishments we are approaching the ideal aimed at in the treatment of any form of tuberculosis, that is, possible maximum immobilization with improved nutrition and immune body supply to the diseased tissues. Bainbridge<sup>14</sup> used oxygen injections following abdominal operations and for the treatment of certain types of tuberculous peritonitis with a view of stimulating tissues, preventing the extension of inflammation, causing increased leukocytosis and phagocytosis, destroying the germs or diminishing their virulence and neutralizing their toxins. Burkhart<sup>15</sup> found in animal experiments that oxygen is an irritant to the peritoneum and is able to increase the reactive capacity of same by bringing about leukocytosis. The symptomatic relief may be immediate or following inflation in 24 to 48 hours. In some cases it may last for 2 to 3 weeks or eventually for a few months in spite of the fact that oxygen is absorbed from the peritoneal cavity in 2 or 3 days. This circumstance indicates that favorable changes are not so much due to the increased abdominal pressure as to the hyperemia that persists after the absorption of oxygen. The relief of the patient with advanced pulmonary tuberculosis from anoxemia and the action of oxygen as a mild cardiac and respiratory stimulant may explain the immediate euphoria seen in some of our patients independently of the local effect of oxygen.

Oxygen or air injection has been used for the treatment of tuberculous peritonitis since 1893. Of the more recent investigators Stein,<sup>16</sup> Mattick<sup>17</sup> and Gilbert<sup>18</sup> consider pneumoperitoneum as a valuable method of treatment for this condition. Laney<sup>19</sup> reports 3 patients with tuberculous enterocolitis, 2 of whom showed great symptomatic relief following pneumoperitoneum. In 1 diarrhea and abdominal pain were relieved by two inflations; in the other, a patient in preterminal stage, 400 cc. of oxygen decreased the diarrhea and greatly relieved the abdominal distress. He states that pneumoperitoneum is such a simple and safe procedure that it should be used more frequently on account of the relief that it affords to patients suffering with intestinal tuberculosis. A similar opinion was expressed by Hayes,<sup>20</sup> with the addition that in early cases it may be instrumental in effecting a cure. He reports that in the 4 cases of ulcerative intestinal tuberculosis, accompanying far-advanced pulmonary tuberculosis, that were treated by diet, intravenous calcium injections and medication without relief, the appe-



tite improved and the diarrhea was reduced from 10 to 20 movements a day to 2 or 3 by oxygen inflation of the abdomen.

This paper is based upon the observations in 44 cases of intestinal tuberculosis treated by pneumoperitoneum during the last 2 years. This number represents a comparatively small percentage of patients with tuberculous enterocolitis in this institution, considering the fact that almost 50 per cent of our admissions are made up of far advanced pulmonary cases. Only patients not showing satisfactory response to dietetic and medicinal treatment were included in this group.

The following brief summary gives detailed information as to the type of case, symptomatology, duration of treatment and end results. The diagnosis was established on the basis of clinical and roentgenologic findings.

**Case Reports.** CASE 1.—F. H., aged 53 years, white, male. Far-advanced pulmonary tuberculosis involving all lobes, of 6 years' duration. Gastrointestinal symptoms: Lack of appetite, nausea, vomiting, abdominal pains, diarrhea, blood in stools for 1 month. January 23, 1929: 400 cc. oxygen; February 15: 800 cc. Much relieved after first treatment. All symptoms gone following second inflation. Symptom-free for 2 years.

CASE 2.—W. R., aged 27 years, white, male. Far-advanced pulmonary tuberculosis, involving both upper and lower lobes for 1.5 years. Gastrointestinal symptoms: Poor appetite, vomiting after meals, abdominal pains, diarrhea for 4 months. January 23, 1929: 200 cc. oxygen; January 30: 800 cc.; February 13: 600 cc.; February 23: 600 cc.; March 13: 800 cc. Result: Appetite much improved, diarrhea ceased, vomiting after meals not as much as before, some gastric distress persisted. Patient died five weeks after last inflation.

CASE 3.—M. S., aged 30 years, white, male. Far-advanced pulmonary tuberculosis, involving all lobes for 3 years. Gastrointestinal symptoms: Nausea, vomiting after meals, constipation alternating with diarrhea began 2 years ago. January 23, 1929: 850 cc. oxygen. Relief from symptoms. Normal stools. Died 3 weeks after treatment.

CASE 4.—P. W., aged 26 years, white, male. Far-advanced pulmonary tuberculosis for 3 years. Gastrointestinal symptoms during last 5 months: Lack of appetite, occasional emesis after meals, cramping pains, constipation alternating with diarrhea. January 26, 1929: 450 cc. oxygen; January 30: 800 cc. Appetite improved, complete relief from other symptoms. Pains returned 6 weeks, and diarrhea 2 months, after treatment. Died 3 months after last inflation.

CASE 5.—S. S., aged 29 years, white, female. Far-advanced pulmonary tuberculosis, involving all lobes for 2 years. Gastrointestinal symptoms: Eructation, nausea, vomiting, severe cramping pains; frequent, very loose, watery stools began 3 months ago. February 1, 1929: 800 cc. oxygen; February 8: 800 cc.; February 15: 850 cc.; February 23: 900 cc.; March 13: 1000 cc.; March 22: 1000 cc.; April 5: 1200 cc. Number of stools decreased from 8 to 12 to 3 to 6 in 24 hours. Consistency of stools somewhat improved. Nausea, emesis and abdominal pain persisted in a less severe form. Discharged against advice.

CASE 6.—C. O., aged 24 years, white, male. Far-advanced pulmonary tuberculosis of 8 months' duration. All lobes involved. Lack of appetite, nausea, vomiting, diarrhea for 1 month. February 1, 1929: 700 cc. oxygen. No relief. Died 2 weeks after inflation.

CASE 7.—R. C., aged 44 years, white, male. Far-advanced pulmonary tuberculosis began 5 years ago. All lobes involved. Gastrointestinal symptoms of 9 months' duration: "Indigestion," constipation alternating with diarrhea, diarrhea predominating. February 6, 1929: 700 cc. oxygen; February 20: 800 cc. Diarrhea ceased, stools became formed. Died 2 weeks after last inflation.

CASE 8.—J. M., aged 52 years, white, male. Pulmonary tuberculosis, involving all lobes, began 14 years ago. Intestinal disease with poor appetite, eructation, nausea, vomiting and abdominal pain for 6 months. February 6, 1929: 800 cc. oxygen; February 20: 800 cc.; March 27: 1000 cc.; May 17: 1200 cc. Complete relief from symptoms with the exception of occasional slight recurrences. Discharged with greatly improved general, pulmonary and intestinal condition 5 months after beginning of treatment.

CASE 9.—M. S., aged 21 years, white, female. Far-advanced pulmonary tuberculosis of 2 years' duration. All lobes involved. Intestinal disease with gastric distress, nausea, vomiting after meals, diffuse abdominal pains, constipation and later on diarrhea developed toward the end of second year. February 8, 1929: 800 cc. oxygen; February 26: 800 cc.; March 22: 1000 cc.; April 22: 1000 cc. No symptoms except emesis following first, and slight abdominal pain following last, inflation. Discharged 3 months after start of treatment.

CASE 10.—F. A., aged 46 years, white, male. Pulmonary tuberculosis, involving all lobes, began 13 years ago. Indigestion, abdominal pain, constipation and diarrhea for 8 months. February 12, 1929: 800 cc. oxygen. No improvement. Died 2 months after treatment.

CASE 11.—M. C., aged 37 years, white, male. Far-advanced pulmonary tuberculosis involving both upper and lower lobes, for 6 years. Intestinal disease, with poor appetite, indigestion, nausea, constipation began 11 months ago. February 12, 1929: 500 cc. oxygen. Relief from gastric distress; constipation persisted. Died 16 days after inflation.

CASE 12.—A. B., aged 39 years, white, male. Far-advanced pulmonary tuberculosis, involving all lobes, for 10 years. Intestinal disease with "indigestion," abdominal pain and constipation during last 7 months. April 9, 1929: 1000 cc. oxygen. No improvement.

CASE 13.—G. D., aged 54 years, white, male. Far-advanced pulmonary tuberculosis of 7 years' duration. Intestinal disease with pyrosis, constipation alternating with diarrhea for 10 months. April 11, 1929: 600 cc. oxygen; April 22: 1200 cc.; May 14: 1400 cc. Pyrosis persisted. Stools normal in frequency and consistency. Died 1 month after last inflation.

CASE 14.—D. B., aged 17 years, white, male. Far-advanced pulmonary tuberculosis of 1 years' duration. Entire left lung and right upper lobe involved. Intestinal disease, with nausea, vomiting after meals, diffuse abdominal pains, diarrhea for 5 months. April 18, 1929: 1000 cc. oxygen; May 9: 1000 cc. No improvement. Died 15 days after last inflation.

CASE 15.—R. N., aged 21 years, white, male. Far-advanced pulmonary tuberculosis began 2 years ago. All lobes involved. Poor appetite and diarrhea for 3 months. April 18, 1929: 1000 cc. oxygen; May 9: 1000 cc.; June 1: 1400 cc.; June 14: 1050 cc.; July 22: 1000 cc. Appetite much better; diarrhea ceased except on the eighth day following second inflation. Appetite became poor after fourth oxygen injection. Diarrhea recurred 9 days after last inflation. Died 2 weeks after last treatment.

CASE 16.—A. K., aged 23 years, white, male. Far-advanced pulmonary tuberculosis involving all lobes for 1 year. Intestinal disease with lack of appetite, gastric distress and diarrhea began 1 month ago. April 30, 1929: 950 cc. oxygen; May 9: 1000 cc.; May 29: 1000 cc.; June 14: 600 cc. No improvement. Died 1 month after last treatment.

CASE 17.—A. L., aged 19 years, white, male. Far-advanced pulmonary tuberculosis of 6 years' duration. "Heart burn," nausea, diffuse abdominal pains and diarrhea for 7 months. May 14, 1929: 1000 cc. oxygen; May 29: 1000 cc.; June 12: 1200 cc.; June 24: 1000 cc.; July 9: 1000 cc.; February 14: 300 cc.; February 21: 600 cc.; March 7: 600 cc. Gastrointestinal symptoms much improved, diarrhea ceased following first five inflations. Complaints gradually reappeared 17 days after treatment was discontinued. No relief was observed by repeated inflations instituted 5 months later. Died 2 weeks after last treatment.

CASE 18.—F. G., aged 19 years, white, male. Far-advanced pulmonary tuberculosis for 1 year. Both upper and lower lobes involved. Gastrointestinal symptoms: Lack of appetite, gastric distress, abdominal pain, cramping in character, diarrhea for 2 months. May 15, 1929: 1000 cc. oxygen; May 29: 1300 cc.; June 12: 1000 cc.; June 24, 1500 cc.; July 9: 1200 cc.; July 23: 1200 cc.; August 13: 1000 cc.; August 31: 1000 cc. No relief. Died 2 weeks after last inflation.

CASE 19.—A. H., aged 39 years, white, female. Far-advanced pulmonary tuberculosis, involving both upper and left lower lobe, for 4 years. Intestinal symptoms began 8 months ago: Nausea, vomiting, severe abdominal pain after meals, diarrhea. June 1, 1929: 600 cc. oxygen. No improvement. Died 2 months after treatment.

CASE 20.—M. H., aged 29 years, white, female. Far-advanced pulmonary tuberculosis for 10 years. All lobes involved. Intestinal disease with poor appetite, gastric pains and diarrhea began 14 months ago. June 1, 1929: 400 cc. oxygen; June 24: 850 cc.; July 9: 1000 cc.; July 23: 1000 cc.; August 13: 1000 cc.; August 27: 1000 cc.; September 11: 1000 cc.; September 30: 1000 cc.; October 14: 1000 cc.; October 28: 950 cc.; November 19: 600 cc.; December 10: 700 cc.; December 21: 500 cc.; January 23, 1930: 500 cc.; February 6: 600 cc.; February 21: 600 cc.; March 15: 500 cc.; March 29: 500 cc.; April 12: 500 cc.; April 26: 500 cc. Complete relief from intestinal symptoms, lasting from 11 to 32 days, when inflation had to be repeated. General and pulmonary condition improved during course of treatment. Inflations were discontinued because of intraabdominal adhesions causing considerable discomfort in last one-third of treatment.

CASE 21.—K. F., aged 45 years, white, male. Pulmonary tuberculosis began 5 years ago. All lobes involved. Gastrointestinal symptoms: Gastric distress following meals, nausea, vomiting, diffuse abdominal pains, diarrhea for 2 months. July 10, 1929: 1000 cc. oxygen; July 20: 1200 cc. No improvement. Died 2 months after treatment.

CASE 22.—L. R., aged 21 years, white, male. Pulmonary tuberculosis, involving entire left lung, with cavitation, began 3 years ago. Intestinal disease with gastric distress and diarrhea for 3 months. July 12, 1929: 1000 cc. oxygen. No improvement. Discharged against advice.

CASE 23.—C. N., aged 29 years, white, male. Far-advanced pulmonary tuberculosis, involving all lobes, for 6 months. Indigestion, abdominal pains, cramping in character, diarrhea for 1 month. July 20, 1929: 1000 cc. oxygen. No improvement. Died 3 weeks after inflation.

CASE 24.—M. X., aged 31 years, white, male. Pulmonary tuberculosis, involving all lobes, began 1 year ago. Gastrointestinal symptoms: Gastric distress, diffuse abdominal pain, constipation alternating with diarrhea, diarrhea predominating for five months. July 22, 1929: 1000 cc. oxygen. Number of bowel movements reduced from 5 to 9 to 2 in 24 hours. Consistency of stools about normal. Relieved from abdominal discomfort. This effect lasted for 23 days, when pain and diarrhea recurred. Died 6 weeks after inflation.

CASE 25.—R. M., aged 27 years, white, male. Far-advanced pulmonary tuberculosis, involving both upper and left lower lobes, for 8 months. Intestinal disease with cramping abdominal pains, most marked in the right lower quadrant, and diarrhea began 3 months ago. September 6, 1929: 1000 cc. oxygen; September 25: 1000 cc.; October 10: 1200 cc. Number of bowel movements decreased from 10 to 13 to 4 in 24 hours. No abdominal pains. Patient's general appearance and mental attitude greatly improved. Discharged against advice.

CASE 26.—H. B., aged 21 years, white, female. Far-advanced pulmonary tuberculosis, involving both upper and lower lobes. Duration of pulmonary disease, 2 years. Gastrointestinal symptoms: Indigestion, abdominal pains, nausea, vomiting, constipation alternating with diarrhea, diarrhea predominating for 2 months. September 30, 1929: 300 cc. oxygen; October 9: 750 cc.; October 23: 800 cc.; November 6: 800 cc.; November 22: 900 cc.; December 6: 1000 cc.; January 7, 1930: 1000 cc. Complete relief from gastrointestinal symptoms. Stools normal in frequency and consistency.

CASE 27.—B. P., aged 23 years, white, female. Far-advanced pulmonary tuberculosis involving all lobes for 1 year. Intestinal disease with lack of appetite, nausea, vomiting after meals, cramping pains, 12 to 14 watery stools daily. October 7, 1929: 550 cc. oxygen. Free from nausea, vomiting and abdominal pain. Stools though watery in character reduced to 6 to 7 in 24 hours.

CASE 28.—F. S., aged 19 years, white, female. Far-advanced pulmonary tuberculosis of 14 months' duration. All lobes involved. Lack of appetite, gastric pain, emesis after meals, pain in right lower quadrant, diarrhea for two months. October 23, 1929: 700 cc. oxygen. Abdominal pains and gastric distress ceased. Stools of better consistency, though not decreased in number. Died 3 months after treatment.

CASE 29.—J. W., aged 30 years, white, male. Far-advanced pulmonary tuberculosis, involving all lobes, began about 1.5 years ago. Intestinal disease with anorexia, pyrosis, nausea, vomiting and diarrhea for 2 months. October 26, 1929: 1000 cc. oxygen. All symptoms disappeared. Stools normal in number and consistency.

CASE 30.—B. W., aged 22 years, white, female. Far-advanced pulmonary tuberculosis, involving all lobes for 8 months. Gastrointestinal symptoms: Anorexia, distress after eating, abdominal pain and constipation developed six months ago. November 8, 1929: 1000 cc. oxygen; November 22: 700 cc.; November 29: 700 cc.; December 6: 750 cc.; December 13: 600 cc. No relief from abdominal symptoms. Constipation ceased. Patient had 2 to 3 loose stools from first to third inflation. One stool of medium soft consistency from that time on until death. Died 2 months from start of treatment.

CASE 31.—W. K., aged 48 years, white, male. Far-advanced pulmonary tuberculosis, involving all lobes, began 3 years ago. Intestinal disease with anorexia, abdominal pain, constipation followed by diarrhea for 7 months. December 5, 1929: 1000 cc. oxygen; December 18: 600 cc.; January 7, 1930: 500 cc.; February 1: 500 cc.; February 14: 300 cc.; March 7: 300 cc. Abdominal pain greatly relieved, though occasionally recurred. Stools not as loose as formerly; no change in their number. Died 5 months after beginning of treatment.

CASE 32.—J. P., aged 58 years, white, male. Moderately advanced pulmonary tuberculosis, involving both upper and right middle lobes, for 1 year. Intestinal disease with gastric distress and constipation began 2 months ago. January 8, 1930: 1000 cc. oxygen; January 23: 500 cc. Relieved from gastric distress and constipation. Constipation recurs occasionally since treatment was discontinued 13 months ago. Patient's general and pulmonary condition is stationary.

CASE 33.—J. G., aged 27 years, Indian, male. Far-advanced pulmonary tuberculosis, involving entire right lung, with cavitation, for 1 year. Indigestion, gastric pain after eating, diffuse abdominal pain for six weeks. No diarrhea or constipation. January 8, 1930: 1000 cc. oxygen; January 25: 750 cc.; February 4: 600 cc.; March 7: 650 cc. Complete relief from symptoms. Symptom-free for 11 months.

CASE 34.—M. W., aged 37 years, white, female. Far-advanced pulmonary tuberculosis, involving all lobes, began 3 years ago. Intestinal disease with indigestion, nausea, flatulence and constipation for 3 months. January 18, 1930: 1000 cc. oxygen; February 6: 1000 cc.; February 21: 800 cc. Normal stools, rarely recurring gastric distress. General and pulmonary condition improved. Discharged 3 months after last inflation.

CASE 35.—M. S., aged 18 years, white, female. Far-advanced pulmonary tuberculosis of 1 year's duration. All lobes involved. Gastrointestinal symptoms: Lack of appetite, cramping pain and diarrhea for 2 months. January 28, 1930: 1000 cc. oxygen; February 6: 1000 cc.; February 21: 800 cc.; March 7: 800 cc.; March 21: 800 cc.; April 8: 600 cc. No improvement.

CASE 36.—E. B., aged 23 years, white, male. Far-advanced pulmonary tuberculosis, involving entire right lung and left upper lobe, began 1 year ago. Intestinal disease with pyrosis, nausea, vomiting, diffuse abdominal pains, diarrhea for 9 months. May 2, 1930: 1000 cc. oxygen; May 13: 1000 cc.; May 20: 650 cc.; June 3: 650 cc.; July 30: 150 cc. Gastric distress and abdominal pains not relieved. Number of stools decreased from 5 to 6 to 2 in 24 hours. All symptoms recurred shortly after treatment was discontinued, in June. When treatment was resumed, in July, the patient's tolerance was so far diminished that further inflations seemed inadvisable. Patient's general, pulmonary and intestinal condition is getting worse gradually.

CASE 37.—B. S., aged 38 years, white, female. Far-advanced pulmonary tuberculosis of 7 years' duration. All lobes involved. Lack of appetite, nausea and vomiting after eating, indigestion, flatulence, abdominal pains, constipation alternating with diarrhea, constipation predominating. May 2, 1930: 1000 cc. oxygen; June 3: 1000 cc.; July 8: 1000 cc.; July 30: 900 cc.; August 27: 850 cc.; September 16: 1000 cc.; September 29: 1200 cc.; October 18: 1200 cc.; November 1: 1200 cc.; November 15: 1200 cc.; November 25: 1200 cc.; December 9: 1000 cc. Relief from abdominal pains and constipation; diarrhea occasionally recurred. Gastric distress after meals persists.

CASE 38.—G. S., aged 37 years, white, male. Far-advanced pulmonary tuberculosis, involving entire right lung and left upper lobe, for 5 years. Intestinal disease with gastric distress after eating, vomiting, abdominal pains, cramping in character, diarrhea for 3 months. May 3, 1930: 1000 cc. oxygen; May 13: 1000 cc.; May 20: 800 cc.; May 27: 900 cc.; June 3: 800 cc. No relief. Died 3 weeks after last inflation.

CASE 39.—R. B., aged 26 years, white, male. Far-advanced pulmonary tuberculosis, involving both upper and lower lobes, began 2 years ago. Intestinal disease with capricious appetite, pyrosis, diffuse abdominal pains and diarrhea for 5 months. May 3, 1930: 700 cc. oxygen; May 13: 800 cc. Complete relief from abdominal symptoms. Stools normal in frequency and consistency. Died 8 days after last inflation.

CASE 40.—J. S., aged 42 years, white, male. Far-advanced pulmonary tuberculosis of 4 years' duration. Both upper and lower lobes involved. Indigestion, abdominal pain, diarrhea for seven months. August 20, 1930: 1000 cc. oxygen; September 2: 1000 cc. Diarrhea disappeared. Slight abdominal pains recurred occasionally. Died 10 days after last treatment.

CASE 41.—T. P., aged 18 years, white, male. Far-advanced pulmonary tuberculosis, involving entire left lung and right upper lobe, for 1.5 years. Intestinal disease with loss of appetite, nausea, vomiting, cramping pains and diarrhea for 6 months. August 27, 1930: 650 cc. oxygen; September 6: 800 cc.; September 9: 900 cc.; September 13: 700 cc.; September 19: 1000 cc.; September 23: 950 cc. Abdominal distress somewhat relieved. Diarrhea lessened; stools less in number but watery in character. Died 1 week after last inflation.

CASE 42.—D. P., aged 21 years, white, female. Far-advanced pulmonary tuberculosis, involving entire right lung and left upper lobe, for 1 year. Intestinal disease with severe abdominal pains and diarrhea for 2 months. August 8, 1930: 1000 cc. oxygen. Number of stools decreased from 3 to 7 to 2 to 3 in 24 hours. Abdominal pain less pronounced. Diarrhea and cramping pains recurred in 6 weeks after inflation. Died 2 months after treatment.

CASE 43.—W. K., aged 21 years, white, female. Far-advanced pulmonary tuberculosis, involving all lobes, began 1 year ago. Intestinal disease with nausea, emesis, diffuse abdominal pain and diarrhea for 1 month. September 16, 1930: 1500 cc. oxygen; September 23, 1200 cc. Free from gastric distress and abdominal pain. Diarrhea ceased. Stools normal in consistency.

CASE 44.—H. O., aged 34 years, white, female. Far-advanced pulmonary tuberculosis of 6 years' duration. All lobes involved. Poor appetite, nausea, vomiting, abdominal pain, constipation alternating with diarrhea for 1 year. September 16, 1930: 700 cc. oxygen. No relief.

TABLE 1.—SYMPTOMATIC RESULTS OF PNEUMOPERITONEUM.

Results.	Number of inflations.										Cases.	Per cent.
	1.	2.	3.	4.	5.	6.	7.	8.	12.	20.		
Complete relief . . . . .	3	6	..	2	1	..	1	..	..	1	14	31.8
Diarrhea ceased, other symptoms persistent . . . . .	..	1	2	..	1	..	..	1	..	..	5	11.3
Diarrhea persistent, other symptoms ceased . . . . .	2	..	..	..	..	..	..	..	..	..	2	4.7
Partial relief from all intestinal symptoms . . . . .	2	..	1	1	2	2	1	..	1	..	10	22.7
No relief . . . . .	7	2	..	1	1	1	..	1	..	..	13	29.6

**Summary.** 1. Forty-four cases of tuberculous enterocolitis treated by pneumoperitoneum are reported.

2. The technique of this procedure is simple and practically without danger.

3. The amount of oxygen and the frequency of the inflations should be adapted to the individual case.

4. The subjective feeling of the patient during operation is a far better indicator than the manometer.

5. The abdomen should rather be underinflated than overinflated.

6. No treatment should be given during the menstrual period.

7. Paradoxical oscillations in the manometer were observed in 3 cases.

8. The abdominal capacity markedly decreased in some cases as the course of treatment progressed.

9. A case of bilateral phrenic nerve block and a case of bilateral artificial pneumothorax simultaneously treated by pneumoperitoneum are cited.

10. The therapeutic effect of this procedure is considered to be due to the direct chemical influence of oxygen, the increased intra-abdominal pressure and the hyperemia of the peritoneum and intestinal serosa.

11. Symptomatic relief was noted in 31 (70.4 per cent) of this group.

12. Complete relief was seen in 14 (31.8 per cent), partial relief from all intestinal symptoms in 10 (22.7 per cent); diarrhea ceased while other symptoms persisted in 5 (11.3 per cent); diarrhea persisted while other symptoms ceased in 2 (4.7 per cent).

13. The duration of symptomatic relief varied from a few days to 2 years.

14. There was no relief in 13, or 29.6 per cent.

15. If it is true that adequate nutrition is the keystone of defense of the body against tuberculosis, the rehabilitation of the subcompetent tuberculous intestines by restoring their normal motility

and digestive function is of prime importance. Our therapeutic efforts should be proportionate to the misery and distress of those suffering with this serious complication. The results of our limited experience are encouraging enough to advocate the more frequent use of pneumoperitoneum in the treatment of intestinal tuberculosis.

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## CHRONIC BASAL NONTUBERCULOUS PULMONARY INFLAMMATION.

### ITS ETIOLOGIC SIGNIFICANCE.

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The following investigation was prompted by the concern shown by parents now visiting clinics and private physicians for possible pulmonary tuberculosis occurring among their children. Although this manifestation which I am about to describe occurs far more

frequently in children, adults are not altogether free.<sup>9</sup> Chronic nontuberculous inflammation of the mucosa along the basal bronchi at first may be looked upon as a benign disease having cough as its chief manifestation; and it is cough<sup>9</sup> that excites the parents' forebodings. Fortunately we can tell some that their concern is needless since cough is an infrequent symptom of childhood tuberculosis, especially if the onset is acute. With this, however, they should not be dismissed; we shall see subsequently that very grave anatomic and pathologic changes may exist.

**Symptomatology.** Many of these patients have no other complaint than cough with expectoration. Acute exacerbations with fever, malaise, hoarseness and an increase in all chest symptoms are common; and it is observed by the parents of the patients as well as by older individuals afflicted with the same disease that these acute attacks are much more frequent than acute colds suffered by their associates. They last 2 days to 1 week and fade into the chronic stage again, with occasional persistent cough and expectoration between attacks. Growth, weight, feeling of well-being and general appearance of the patient do not suffer any interference.<sup>9</sup> Ochsner and Nesbit<sup>13</sup> described a mild neurosis accompanying this condition later in life when bronchiectasis developed.

**Physical Examination.** During the chronic stage there are only a few physical signs indicative of this disease. A mild pharyngitis is common; tonsillitis and facial sinusitis is no more common than in normal individuals, and when present is likely to be a response to secondary infection from the basal bronchi; thoracic contour is not altered; breathing may be a little more frequent and deeper than normal; there is seldom clubbing of the nails. A mild impairment of the percussion note over the bases may exist. Tactile fremitus, vocal resonance and expansion are not disturbed, but the breathing may be harsh. Crepitant râles are usually present,<sup>3</sup> and these are increased in number when elicited in the manner of pertussis râles. During the acute stages râles are always present; between attacks, contrary to Stewart's<sup>3</sup> observation, they may disappear completely. These râles are located over the bases posteriorly or laterally.<sup>3</sup> When they are found throughout the chest a generalized bronchitis exists. Waldbott<sup>16</sup> described an allergic bronchitis that is confused with other forms of pulmonary disease.

**Laboratory Examinations.** The sputum is densely purulent during the acute stages and may become scropurulent during remissions. Pus cells and the various organisms found along the respiratory tract are present when microscopic examination is made. No one organism seems to predominate; spirochetes and fusiform bacilli are uncommon and seem to have no significance. Charcot-Leyden crystals and Curschmann's spirals are not present.

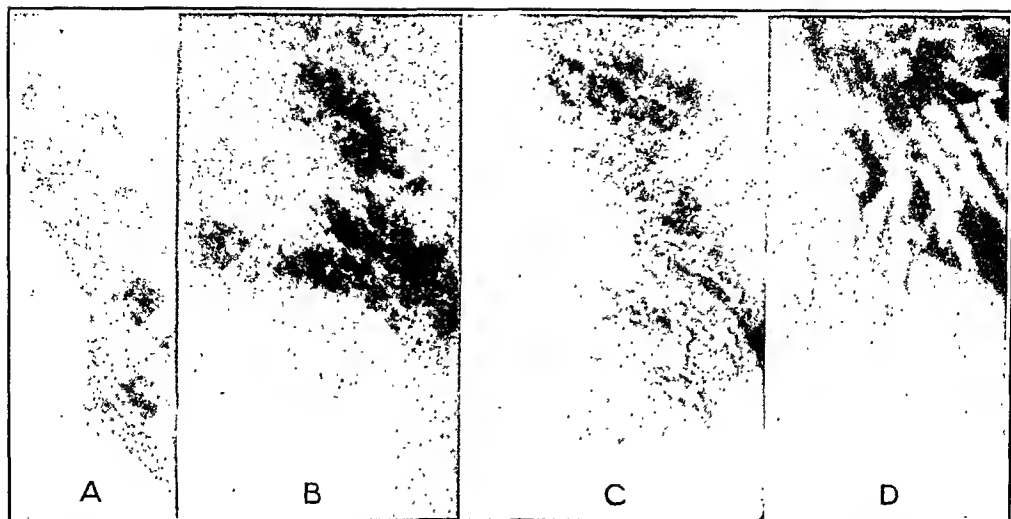


FIG. 1.—A, Left bronchi slightly widened; symptoms characteristic. A boy aged 10 years. B, At first signs of lung abscess of the left base; rapid improvement, with disappearance of expectoration and râles. Widening confined entirely to the left base. Girl aged 13 years. C, Free of cough; postural drainage did not produce sputum. Widening confined to left base. Girl aged 18 years. D, Male, 30 years, having all the symptoms of frank bronchiectasis. Probably a congenital widening and permanently infected, with irradicable cough. Lung abscess is the brigand in the dark awaiting them.

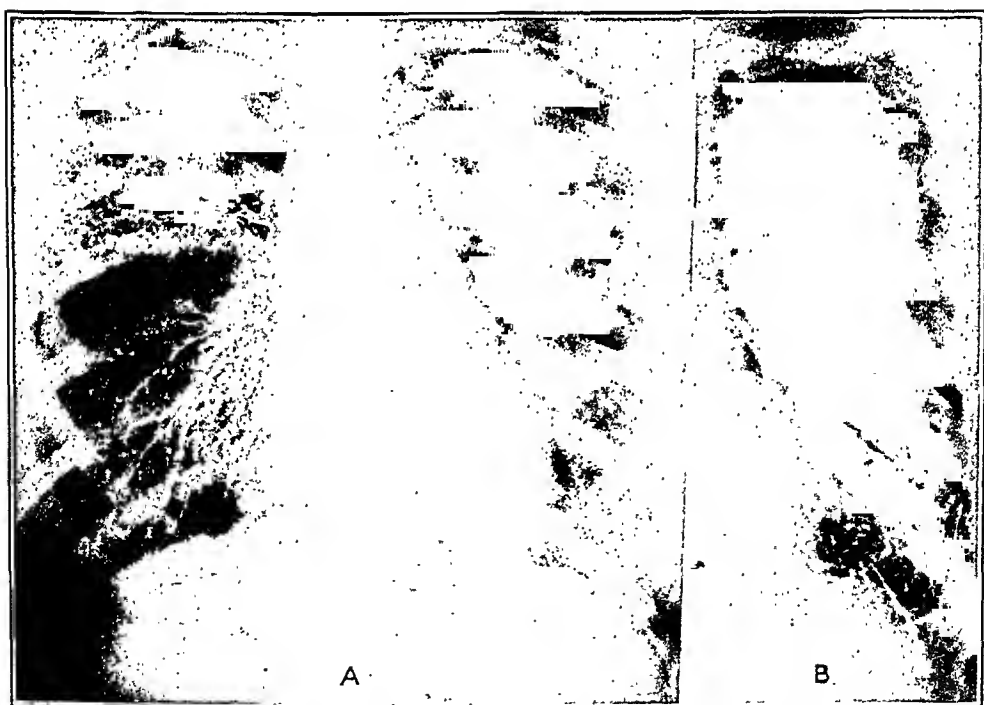


FIG. 2.—A, Roentgenogram showing normal bronchi on the right side and slight widening of the bronchi on the left. This patient had all the signs of chronic basal inflammation due to widening. She was twenty-five years of age and had been troubled with attacks of productive cough since childhood. Subsequent lipiodol introduction revealed the bronchi extending into the costophrenic angle on the left side to have reached a pathologic change. B, An asthmatic bronchus.





*Roentgenologic Examination.* Single or stereoscopic films without lipiodol injection may show nothing. If the patient has not coughed and expectorated for several hours before<sup>8</sup> films are taken or if the patient is having an acute reactivation at the time, there may be indistinct areas of increased opacity along the basal trunks. Miller and Eglee<sup>8</sup> are of the same opinion, while Hebert<sup>6</sup> found increased translucency due to emphysema. Since the introduction of lipiodol by Sicard and Forestier<sup>18</sup> much of the uncertainty associated with pulmonary skiagraphy has been overcome and in no instance has its differential benefits been more revolutionizing than in basal pulmonary inflammation. Until now the syndrome has been treated as a single entity. Early in the life of the patient, and from a physical and symptomatic standpoint, no other course could have been possible; but as a result of frequently resorting to bronchography, I have been able to prove conclusively that 62 per cent (Fig. 1) of this series have underlying anatomic changes—bronchial widening—responsible for this clinical syndrome; I have been able to record various stages of widening at different ages so that it would seem beyond doubt that anomalous development is the initiating factor in these cases. The other 38 per cent were found not to have widening, and it is my opinion that these cases never progress into widening and “clinical bronchiectasis” as do the former. In fact, they seem to have the asthmatic type of of bronchus. (Fig. 2, B.) Thus we have two groups: the former, a grave change; the latter, a benign state of lesser importance. So distinctly are the two divided that the following classification is proposed:

Chronic basal nontuberculous pulmonary inflammation.

(a) With bronchial widening.

(b) Without bronchial widening.

It was observed by Ochsner,<sup>15</sup> Sauerbruch,<sup>2</sup> Grawitz<sup>1</sup> and Duken<sup>10</sup> that widening of the bronchi most frequently occurred on the left. Duken thought<sup>10</sup> that the left pulmonary artery constricted the left main bronchus before the superior branch came off and that the lower branch most commonly came off at an acute angle, all of which would tend to facilitate dilatation. To these suggestions I would like to add the possible influence of a continuously stimulated vagus nerve. The left vagus passes anterior and lateral on the aortic arch, where it may be pounded upon by this pulsating structure, thus stimulating it to dilate the bronchi of its distribution which prolonged would facilitate their abnormal development. This series which was composed almost entirely of children consisted of 50 per cent unilateral left-sided dilatation. That abnormal widening of the basal bronchi has a congenital origin seems undisputable. Grawitz,<sup>1</sup> Sauerbruch,<sup>2</sup> Duken,<sup>10</sup> Meyer<sup>7</sup> and Henschen<sup>7</sup> were of this opinion. Dunham<sup>17</sup> demonstrated malformation of the

entire left bronchial tree. When injected with lipiodol the bronchi were found to simulate the budding of the embryologic stage.

Immediately it is suggested that these cases with widening go on to develop clinical bronchiectasis which they do.<sup>3,8,15</sup> This change is slow in some instances and rapid in others, depending possibly on the frequency of reinfection, daily hygienic surroundings, occupation and the supervening of pertussis, measles or influenza. One of this series was well until the age of 8 years, when he developed pertussis and failed to recover from the cough; Steidel's<sup>14</sup> case gave no symptoms until the age of 25 years, at which time he became infected and had hemoptysis; Villaret's<sup>11</sup> case was free of symptoms until the age of 32 years; another of this series (Fig. 1, C) at the age of 18 years had only periodic attacks of productive cough. During remissions she has been entirely free of cough and expectoration. These cases are strongly confirmative of Bezancon's<sup>12</sup> description of dry bronchiectasis. Ochsner,<sup>9,15</sup> Miller<sup>8</sup> and Eglee<sup>8</sup> were of the opinion that abnormal widening of the bronchi disposed to basal bronchitis and bronchiectasis. These men have worked chiefly on adults. Stoney<sup>5</sup> thought pyorrhea alveolaris frequently was associated with chronic basal bronchitis; Graves, Foster and Hett<sup>4</sup> considered humid and unhygienic surroundings as the most common cause of chronic bronchitis. We find that there are several factors tending to produce chronic basal bronchitis, but the important thing to remember is that bronchial widening is a frequent cause, and when present the prognosis is greatly altered.

*Differentiation of the Two Types.* Frequent reference has been made to describers of chronic basal bronchitis who believe that congenital widening of the bronchi is an etiologic factor and predisposes to bronchiectasis. The symptomatology of the syndrome has been described; but an investigation for differential purposes and a study of these cases of bronchial widening prior to development of clinical bronchiectasis has been but little studied. I maintain that an early differentiation of the two should be made, for the treatment and prognosis is entirely different.

The only reliable way to differentiate the two is by means of bronchography. Should Roentgen facilities be inaccessible the following are good differential points: If widening exists the cough is apt to be more productive, more chronic; the sputum will be more purulent, and when the patient is put in a position for draining the basal bronchi and told to cough, considerable brownish-yellow or greenish sputum may be produced. This is during attacks; between attacks the sputum may disappear completely. These signs are not entirely reliable.

**Conclusions.**—1. Basal pulmonary inflammation as described above is nontuberculous.

2. These cases can be grouped as follows: (a) With bronchial widening; (b) without bronchial widening.

3. When widening exists it is much more common on the left; there are strong indications that anomalous development is the cause, and the prognosis is grave.

4. When widening is absent the chances for recovery are assured.

5. There is no specific organism responsible.

#### SUMMARY OF CASES.

	Negative.	Positive.			
Mantoux test . . . . .	4*	19			
Family history of pulmonary tuberculosis . . . . .	19	4			
Upper respiratory infection . . . . .	14	9			
			L.	R.	R.&L.
Congenital widening . . . . .	9	12	0	2	
Average age . . . . .	13.5 yrs.	(Oldest 33 yrs. and youngest, 6 yrs.)			

\* Figure is number of cases. Total number of cases was 23.

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## TUBERCULOSIS SIMULATING ACUTE LEUKEMIA.

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As a definite relationship between tuberculosis and leukemia has never been established, we present 2 cases to illustrate that a tuberculous infection may produce a clinical picture simulating an acute myeloid leukemia.

Since 1924, 86 cases diagnosed as leukemia have been studied at the Long Island College Hospital and 11 of these showed the presence of pulmonary tuberculosis with leukemoid blood pictures. Nine of these cases are not included in this report because of the absence of postmortem examination.

Patients suffering from chronic leukemia may die of pulmonary tuberculosis and occasionally pulmonary tuberculosis may give rise to a qualitative or a quantitative increase in lymphatic cells. Joachim<sup>1</sup> reported a case illustrating that leukemia may give rise to infiltrations of the lung simulating tuberculosis.

The bizarre blood reactions seen in agranulocytosis, in acute mononucleosis and in certain cases of severe infections of non-leukemic origin, are proof that too much reliance cannot be placed upon the blood picture alone.

The difficulties encountered in the final interpretation of these cases are:

1. Did the patients have myeloid leukemia with tuberculosis as a complication?
2. Did they have tuberculosis which so affected the hemopoietic system as to give rise to a leukemic blood picture?

As far back as 1896, Volpe<sup>2</sup> discussed the association of tuberculosis and leukemia and in 1902 Quinke published a case report illustrating this association. Many observers stress the frequent occurrence of tuberculosis with leukemia and in 1913 Nanta<sup>4</sup> collected 37 cases of myeloid leukemia and tuberculosis.

The consensus of opinion is that tuberculosis is superimposed upon the leukemia and the tuberculosis becomes active after the body resistance has been lost because of leukemia.<sup>6,7,8</sup>

Mönckeberg<sup>3</sup> suggests that tuberculosis may so alter the leukemic

reaction that at autopsy one may not find anything characteristic of the leukemia.

**Case Reports.**—CASE 1. G. S., a white female, aged 30 years, entered the Long Island College Hospital complaining of vaginal bleeding and weakness for 3 months. At the regular menses the flow lasted 10 to 15 days instead of the usual 4 to 5. Between periods spotting was present and at autopsy this bleeding was found to be due to an eroded pedunculated fibroid. The weakness, gradual in onset and described as an early fatigue, had become so severe that the patient was confined to bed. The family history as well as the past personal history disclosed nothing of note.

**Physical Examination.** A young, adult female showing good nutrition but a definite pallor. Temperature, 101.2° F.; pulse, 100; respiration, 20; blood pressure, 100 systolic and 60 diastolic. Fifteen to 20 small, discrete lymph nodes, 1.5 cm. in size, were present at either side of the neck. Harsh bronchovesicular breath sounds with small bubbling râles on deep inspiration were heard at both upper lung lobes. Neither liver nor spleen was palpable. The vaginal bleeding was present.

**Laboratory Findings.** The Wassermann reaction was negative. The urine showed a specific gravity of 1020, no albumin, no sugar. Microscopic examination of a catheterized specimen was negative. Blood chemistry: sugar, 110 mgm.; urea, 28.1 mgm.; uric acid, 3.4 mgm.; creatinin, 1.3 mgm. Blood culture was sterile. Throat culture showed a hemolytic streptococcus. Sputum examination was negative for tubercle bacilli. Roentgen ray of chest revealed "tuberculous changes" scattered throughout both lungs.

**Clinical Course.** Weakness and restlessness were the outstanding symptoms. The vaginal bleeding responded only temporarily to blood transfusions. Temperature was intermittent, varying between 101° and 105°. There was marked respiratory difficulty and extreme exhaustion upon the slightest exertion. Pulse was 120 to 160 and respirations were 20 to 40. Air hunger and stupor were the outstanding terminal symptoms.

TABLE 1.—BLOOD FINDINGS OF CASE 1.

Date.	R. B. C. per c.mm., in millions.	W. B. C. per c.mm., in thousands.	Hgb., per cent.	Platelets per c.mm.	Ret., per cent.	N.P., per cent.	S.M., per cent.	My. O.P., per cent.	My. O.N., per cent.	N. My., per cent.	U.C., per cent.	Bl. T., minutes.
November 10 . .	2.4	7.0	50	130,000	1	2	6	20	53	13	6	8
*November 13 . .	2.9	5.2	54	....	..	9	..	58	23	10	10	
*November 20 . .	..	5.7	62	....	..	5	..	52	20	13	10	
November 25 . .	..	7.4	68	....	..	3	..	80	12	5	5	
December 1 . .	2.2	24.0	..	....	..	2	..	74	5	19	0	
December 6 . .	..	2.8	42	....	..	3	..	72	12	13	0	

Ret. = reticuloeytes. N.P. = neutrophilic polymorphonuclears. S.M. = small mononuclears. My. O.P. = myeloblasts oxidase positive. My. O.N. = myeloblasts oxidase negative. N. My. = neutrophilic myeloeytes. U.C. = unidentified cells. Bl. T. = bleeding time.

\* Confirmed by Dr. Florence Sabin.

*Autopsy.* All of the organs showed marked anemia. The outstanding pathologic findings were confined to the lungs.

Both *lungs* were considerably smaller than normal and extremely irregular in outline, due to alternately areas of fibrosis and emphysema. Both apices contained old scars. Throughout both upper lobes, the upper portions of both lower lobes and the entire right middle lobe was a fine fibrosis producing a coarsely alveolar structure. Along the lower margin of these areas was a clearly demarcated line of advance of the sclerosing process, apparently fibroid phthisias. Near the base of the right lower lobe was a calcified nodule which was probably the primary focus. An area of hemorrhagic bronchopneumonia in the right lower lobe was covered by a thin layer of fibrinous pleurisy.

*Microscopically*, the extensive fibrosis was found to be due to a sclerosing tuberculosis. At the margin of the process were well-formed tubercles containing giant cells. Tubercle bacilli were found in these areas. Surrounding the tubercles and in areas adjacent to the tuberculous foci there was a mononuclear reaction, the cells consisting of lymphocytes and myelocytic cells. In the bronchopneumonic area, the exudate in the alveoli consisted of fibrin, red cells, and mononuclear cells but showed a complete absence of polymorphonuclears.

The *spleen* weighed 190 gm. and showed the gross picture of acute splenic tumor. *Microscopically*, the Malpighian corpuscles were small and densely packed with lymphocytes. The pulp was congested and scattered throughout were lymphocytes and myelocytic cells in about equal numbers. Most of the latter showed a nongranular cytoplasm and appeared to be myeloblasts. A few were definitely granular and were interpreted as myelocytes. Scattered megakaryocytes were also found.

The *liver* weighed 1900 gm. Its normal markings were well retained. There was a slight increase in its fat content and a moderate degree of congestion. *Microscopically*, the sections showed cloudy swelling, slight fatty infiltration and congestion. There was only a mild cellular infiltration, consisting of normal lymphocytes, in the portal canals and among the liver cords.

The mesenteric and retroperitoneal *lymph nodes* were somewhat prominent. *Microscopically*, they showed moderate congestion and edema. They contained a good many myelocytic cells but in smaller numbers than in the spleen.

The *kidneys* showed only slight passive congestion and cloudy swelling of the convoluted tubules.

In the cavity of the *uterus* a large pedunculated polyp was found. Its surface was eroded and intensely hemorrhagic.

The *ribs* contained red marrow. The predominant cells were myeloblasts. Very few myelocytes and no polymorphonuclear leukocytes were present.

The *tibia* contained yellow marrow.

The other organs showed no gross or microscopic pathology of note. There was no leukemic infiltration beneath any of the serous surfaces.

CASE 2.—An adult male, aged 30 years, entered the Long Island College Hospital complaining of fever (100° to 103° F. for 2 weeks), cough, and weakness. The cough had been present for 3 weeks and was accompanied by blood-streaked expectoration. The weakness was such that the patient was unable to walk. The family history as well as the past personal history was negative.

*Physical Examination.* An adult male, acutely ill and unable to give a detailed history. Temperature, 103.2° F.; pulse, 120; respiration, 26; blood pressure, 80 systolic and 40 diastolic. Nutrition was poor, skin was moist. The mucous membranes were very pale. The posterior cervical group of lymph nodes were enlarged, partly coalesced and tender. Six to 8 1- to 2-cm. sized nodes were present in either groin. The lungs showed diffuse harsh bronchovesicular breathing with many sibilant and sonorous râles throughout the entire thorax. Dullness was present at the right upper lobe. The spleen was felt at the level of the umbilicus. The liver was not palpable.

*Laboratory Findings.* The Wassermann test was negative. The urine showed a trace of albumin, no sugar, and 3 to 6 white blood cells per low-power field. Blood chemistry: sugar, 105 gm.; urea, 22.9 mgm.; uric acid, 2.8 mgm.; creatinin, 1.25 mgm. Blood culture was sterile. Sputum was found to contain a pneumococcus type 4 and a streptococcus hemolyticus; no tubercle bacilli were found in 8 consecutive sputum examinations. Roentgen ray of chest was interpreted as pneumonia, right upper lobe, very probably tuberculous.

*Clinical Course.* The temperature was continued in type for 10 days; the remainder of the time it was intermittent, varying from 100.8° to 103.4° F. The spleen remained enlarged. The lung findings were those of a broncho-pneumonia. The patient expired 3 weeks after admission.

TABLE 2.—BLOOD FINDINGS IN CASE 2.

Date.	R. B. C. per c.mm., in millions.	W. B. C. per c.mm., in thousands.	Hgb., per cent.	Platelets per c.mm.	N.P., per cent.	S.M., per cent.	L.M., per cent.	My., per cent.	N. My., per cent.	Eo. My., per cent.	U.C., per cent.
June 18 . . . . .	2.84	57	38	160,000	39	4	2	15	35	3	2
June 22 . . . . .	...	68	34	...	21	3	5	12	30	4	5
June 25 . . . . .	2.56	65	30	...	23	2	6	9	52	3	5
July 2 . . . . .	...	26	50	150,000	36	3	1	5	50	5	0
July 10 . . . . .	2.13	7	40	...	18	2	2	9	65	4	0

N.P. = neutrophilic polymorphonuclears. S.M. = small mononuclears. L.M. = large mononuclears. My. = myeloblasts. N. My. = neutrophilic myelocytes. Eo. My. = eosinophilic myelocytes. U.C. = unidentified cells.

*Autopsy.* The only striking external feature was a marked fullness of the right thorax.

The right upper and middle lobes of the lung were firmly consolidated and their pleural surfaces covered with a thin layer of fibrin. The consolidation was due to a tuberculous pneumonia. Large irregular areas of caseous pneumonia were separated by areas of gelatinous pneumonia. Scattered throughout the right lower lobe and the entire left lung were small caseous nodules ranging from 1 to 5 mm. in diameter. Near the anterior margin of the middle lobe was a small depression beneath which was a calcified nodule, the primary focus. The hilar and mediastinal lymph nodes were greatly enlarged and almost entirely caseous. The lower half of the trachea and both main bronchi were diffusely ulcerated.



*Microscopic examination* confirmed the above gross findings. A conspicuous feature was the almost complete absence of productive changes. The tuberculous areas were completely necrotic with little or no epithelioid reaction and no lymphocytic or fibroblastic zones. Tubercle bacilli were present in enormous numbers.

The *heart* was small and flabby. The valves and great vessels were grossly normal.

The *spleen* was greatly enlarged and weighed 1170 gm. The normal configuration was in general retained. It was very firm in consistency with moderately thickened capsule through which could be seen scattered irregular areas of necrosis. The surface on cut section showed innumerable miliary tubercles and irregular shaped areas of infarction.

*Microscopically* there was a moderate degree of fibrosis throughout. The Malpighian corpuscles were almost entirely missing and those remaining were very small and indistinct. The miliary tubercles noted in the gross, consisted of areas of caseation necrosis with narrow epithelioid margins. No peripheral lymphoid or fibrotic zones surrounded these areas and they contained very few giant cells. The pulp was moderately congested and contained many megakaryocytes, large numbers of lymphocytes, myeloblasts, and smaller numbers of myelocytes, erythroblasts and polymorphonuclears. The cells appeared in varying proportions in different areas.

The retroperitoneal and mesenteric *lymph nodes* were moderately enlarged. *Microscopically* they contained myelocytic cells but in much smaller numbers than in the spleen.

The *marrow from the ribs* was very fibrotic. Focal cellular areas contained lymphocytes, myeloblasts and myelocytes in varying proportions. A good many megakaryocytes were also found.

The *liver* was normal in size and shape but heavily studded with miliary tubercles. Surface and cut section otherwise showed no gross pathology. Unfortunately no microscopic study of the liver was made.

The *kidneys* were grossly normal except for cloudy swelling. No tubercles were grossly visible. *Microscopically* there was found a slight passive congestion and cloudy swelling of the convoluted tubules. No tubercles appeared in the section studied. There was no cellular infiltration in any of the renal tissues.

The *gastrointestinal tract* showed no lesions of note. No tuberculous ulcers were found in the ileum, cecum or colon.

The remaining viscera were grossly normal. No gross leukemic infiltration was found beneath any of the serous surfaces.

**Discussion.** The modern conception of the hemopoietic tissues as a system, together with the newer methods of study of this system, lead us to believe that these tissues may occasionally respond to any infection in such a way as to produce a leukemic blood picture.<sup>9</sup> Some infections give rise to leukopenia, others to leukocytosis, and still others to an agranulocytosis. No one specific organism alone is responsible for such individual reactions.

One is very seldom justified in making a diagnosis from the blood picture alone. Not only must the history and the physical findings of the patient be correlated with the blood picture, but often a

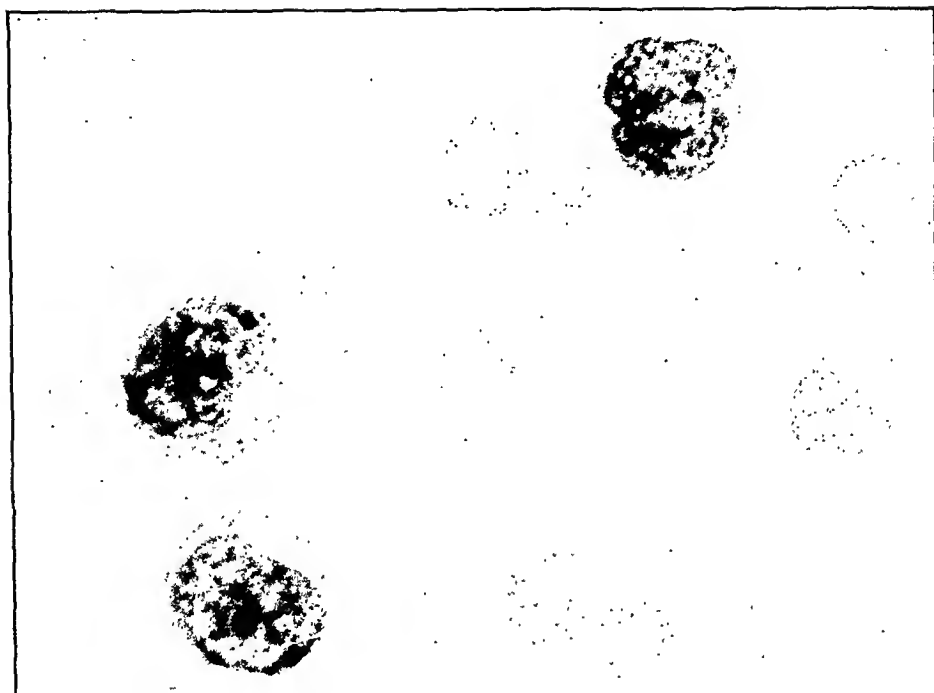


FIG. 1.—Case 1. A field showing three myeloblasts. Wright stain.  $\times 1100$ .

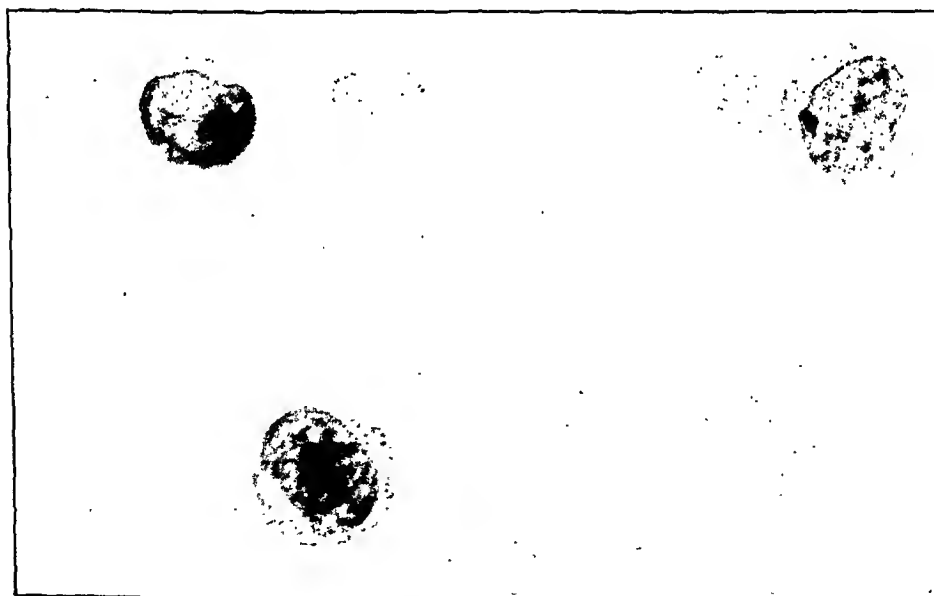


FIG. 2.—Case 1. A field showing three myeloblasts. Oxidase stain.  $\times 1100$ .

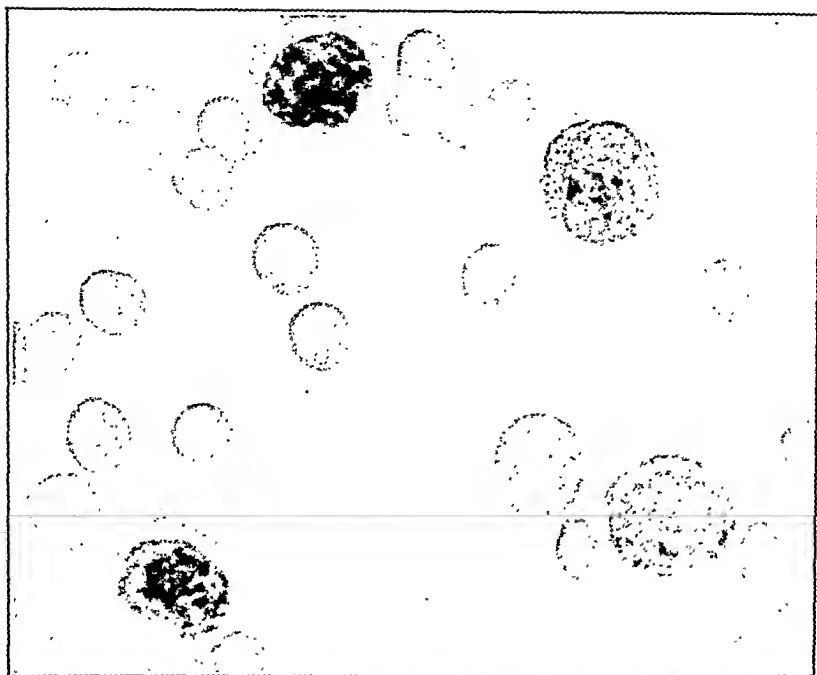


FIG. 3.—Case 2. A field showing three myeloblasts and one metamyelocyte. Wright stain.  $\times 1100$ .

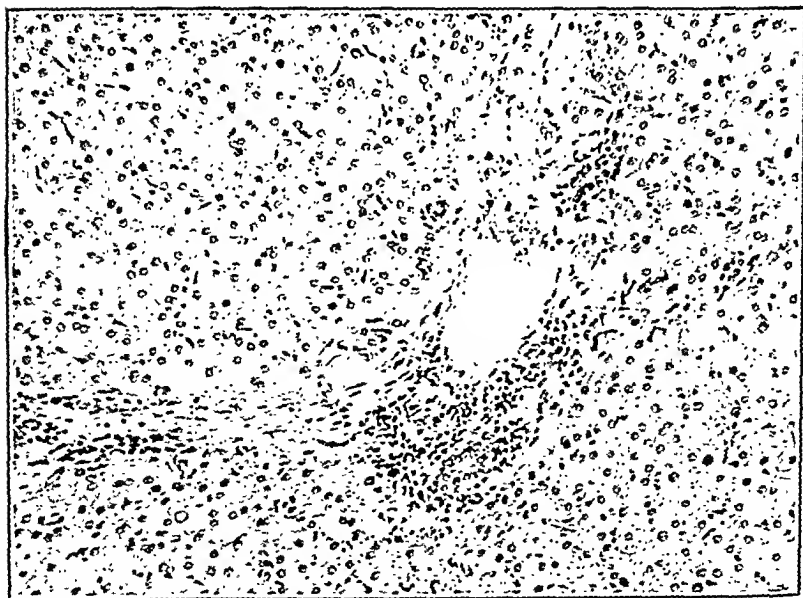


FIG. 4.—Case 1. Section of liver showing absence of typical leukemic infiltrations.  $\times 300$ .



FIG. 5.—Case 2. Section of hilar lymph node showing an area of caseation necrosis surrounded by an ill-defined epithelial zone.  $\times 100$ .



FIG. 6.—Case 2. Section of a nontuberculous lymph node showing large numbers of myelocytic cells and an occasional megakaryocyte.  $\times 300$ .



FIG. 7.—Case 2. Section of rib marrow showing diffuse fibrosis, moderate numbers of myeloid cells, several megakaryocytes and an occasional nucleated red blood cell.  $\times 500$ .

study of the patient's clinical course and final outcome are necessary for the proper final interpretation of that particular case.

In the above reported cases the presence of tuberculosis was the outstanding feature of the postmortem findings. There was absence of characteristic leukemic infiltrations in the tissues, and the spleen, and bone marrow showed only a moderate myeloid hyperplasia, such as one might find in various nonleukemic conditions. Tubercle bacilli were demonstrated in the tissues.

Clinically both patients presented an acute illness of a short duration and therefore the presence of either chronic tuberculosis or chronic myeloid leukemia seemed unlikely. If they had been available for study over longer periods, a more conclusive opinion could have been reached on this point. The severity of the condition associated with a profound anemia and a myeloid blood picture might have justified a clinical diagnosis of acute myeloid leukemia. However, the usual hemorrhagic manifestations were absent. There were neither purpuric spots nor mucous membrane hemorrhages. In the first case there was neither hepatic nor splenic enlargement. In both cases there existed physical signs of pulmonary tuberculosis.

**Conclusions.** 1. Tuberculosis may so affect the hemopoietic tissues as to give rise to a myeloid leukemic blood picture.

2. We present 2 cases of tuberculous infection, 1 pulmonary, the other generalized, with a myeloleukemoid blood picture and a clinical course simulating acute myeloid leukemia.

**NOTE.**—The authors wish to express their thanks and appreciation to Dr. Florence Sabin for her aid in identifying the blood cells in Case 1, to Dr. E. B. Krumbhaar and to Dr. L. F. Warren for their coöperation in the interpretation of the above reported cases.

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## CARBOHYDRATE METABOLISM IN RELATION TO POST- OPERATIVE CRISES IN HYPERTHYROIDISM.\*

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THE vagaries of the thyroid gland present many matters that deserve thoughtful consideration, and there are many problems relating to the toxic goiter still unsolved. There is general agreement as to the propriety of surgical treatment in the majority of cases; there is no disagreement as to the essentials of the operative program. There are today, it seems to me, two problems of transcending importance, one which has to do with the arrest of the hyperplastic process once it is recognized; the other, with the elimination of operative hazards. In Lugol's solution we have a therapeutic measure which acts like a specific but only for a limited time. What must we add to or substitute for Lugol's solution to render the results permanent? With the exception of the hazards of operation that have to do with the cardiac mechanism, the greatest and most disturbing to me has been the postoperative crisis. Two-thirds of our fatalities are attributed to this, and once a serious crisis is established our efforts to control it have been almost futile. I propose to take for my theme today carbohydrate metabolism and postoperative crises.

The last two decades have added greatly to our knowledge of the physiology of the glands of internal secretion, but there remains still much which we must know before a definite conception of the interrelationship of these structures can be formulated. Within recent years physiologists have attempted to demonstrate the close relationship between the various structures which pour their secretory products into the blood stream, but until we understand more clearly the exact function of each gland and motivating force or forces which bring it into play with other glands, our knowledge of coöperative effect and correlation must be limited. Cannon, more than any other American physiologist, has contributed to this subject. He has suggested the interrelationship between the thyroid and the adrenals, and he has presented evidence which must become more and more important.

For some years I have been much interested in the varying postoperative reactions of the hyperthyroid patient. Why is it that there are such extraordinary variations in the reactions following operation? To be sure we are reasonably certain that the

\* An address before the American Association for the Study of Goiter, Kansas City, Missouri, April 9, 1931.

more serious reactions are associated with the highest degree of toxicity. But one can never foretell or forecast a crisis that may threaten the patient's life. It has been said that such reactions may be due to an excess of thyroxin thrown into the circulating blood as a result of the operation, but you well remember crises in the days before the administration of Lugol's solution, when only the superior thyroid vessels may have been ligated and the amount of trauma to the glands negligible.

Four years ago, following the isolation of histamin and cholin from certain structures by Best and others,<sup>1</sup> we utilized a similar technique for their extraction from various types of thyroids. In these we were unable to demonstrate the presence of either of these vasodepressor substances in greater amount per gram of gland in the thyroid adenoma or hyperplastic goiter than that found in the simple colloid goiter. The experiments were clear cut and left no doubt in our minds that these substances could in any way be responsible for the varying reaction observed after operation on the patient for thyroid disease.

However, certain suggestive leads have been published from time to time which may not be amiss to mention here. Schliephake<sup>2</sup> has found that after thyroidectomy dogs are more sensitive to acetylcholin and less sensitive to adrenalin, as measured by their effects on the blood pressure and on the electrocardiogram. When, however, the animals were fed thyroid extract their normal sensitivity to these drugs was restored. It is, therefore, possible that a similar amount of cholin may produce more definite effects in thyroidectomized patients.

Of considerably more interest to me has been a study of the carbohydrate metabolism during the hyperthyroid state. The relationship which thyroid secretion has to the liver and adrenals and possibly also to the pancreas has attracted the attention of many investigators. Cannon and Britton have on a number of occasions referred to the effect of emotional states on the production of glycosuria and hyperglycemia, and Bowman and Kasanin<sup>3</sup> have reviewed this subject thoroughly both from its physiologic and clinical aspects.

Holst,<sup>4</sup> who has made many contributions to the subject of thyroid dysfunction, published, in 1921, the autopsy studies in 4 cases of exophthalmic goiter associated with glycosuria. In these he found a decrease in the islands of Langerhans. Numerous investigators have recognized the fact that experimental diabetes produced by partial extirpation of the pancreas is to an extent controlled by thyroidectomy. Falta<sup>5</sup> found that thyroidectomy is followed by hypertrophy of the islands of Langerhans. Although, in the many observations which appear in the literature there seems to be some conflict, yet the weight of the evidence seems to be that pancreatic and thyroid function affect each other closely. In



support of this contention, certain authors have described a hyperglycemia after operations for hyperthyroidism, but this evidence is not conclusive, since hyperglycemia may occur after any operation where general anesthesia has been used.

Rosenberg<sup>6</sup> carefully studied the glucose-tolerance curves in patients with exophthalmic goiter. He believed that sugar excretion was increased in this disease, but the tolerance curves do not parallel the severity of the clinical symptoms. With both of these deductions John<sup>7</sup> agrees, in that he has obtained similar curves after glucose-tolerance studies, and he states that his findings suggest "an increased permeability of the renal filter during active hyperthyroidism."

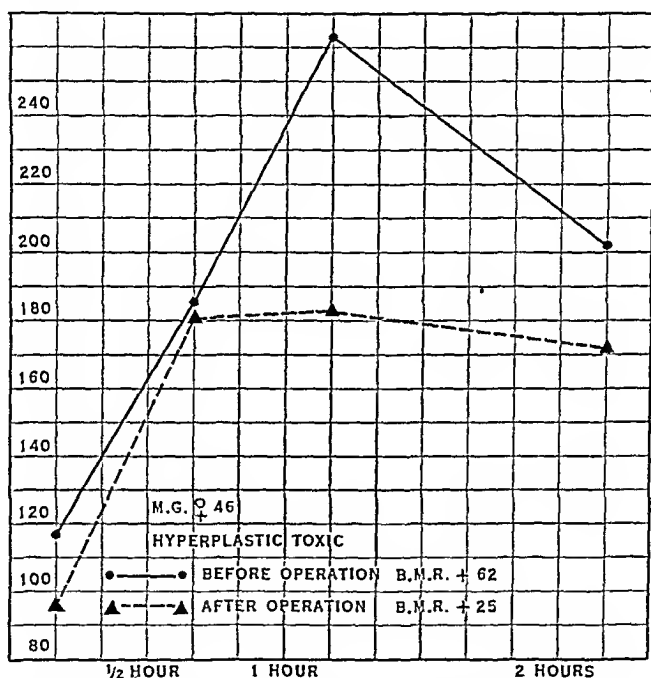


CHART I.—Curve of blood-sugar levels during glucose-tolerance tests before and after thyroidectomy on a patient with hyperplastic toxic goiter.

As illustration, here are three fairly representative glucose-tolerance charts from our series in thyrotoxic patients. The customary technique was followed: First taking a fasting blood sugar (venous), then administering 75 gm. of glucose by mouth, then taking blood sugar at  $\frac{1}{2}$ -, 1- and 2-hour intervals. It will be noted there is considerable variation in the basal rates of these patients, both before and after operation.

One of the most interesting observations bearing on this subject has been made by Marks<sup>8</sup> of Dale's laboratory. He found that a

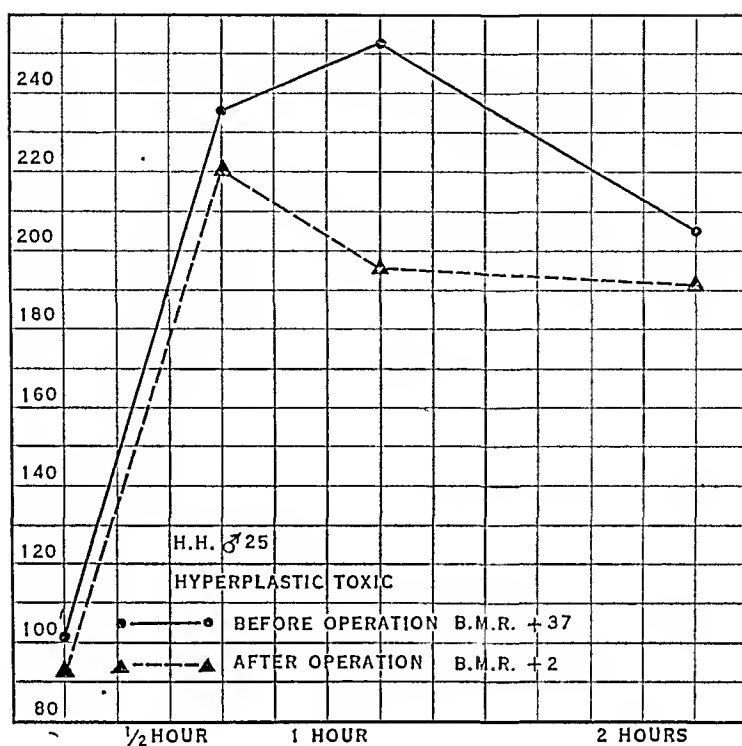


CHART II.—Curve of blood-sugar levels during glucose-tolerance tests before and after thyroidectomy on a patient with hyperplastic toxic goiter.

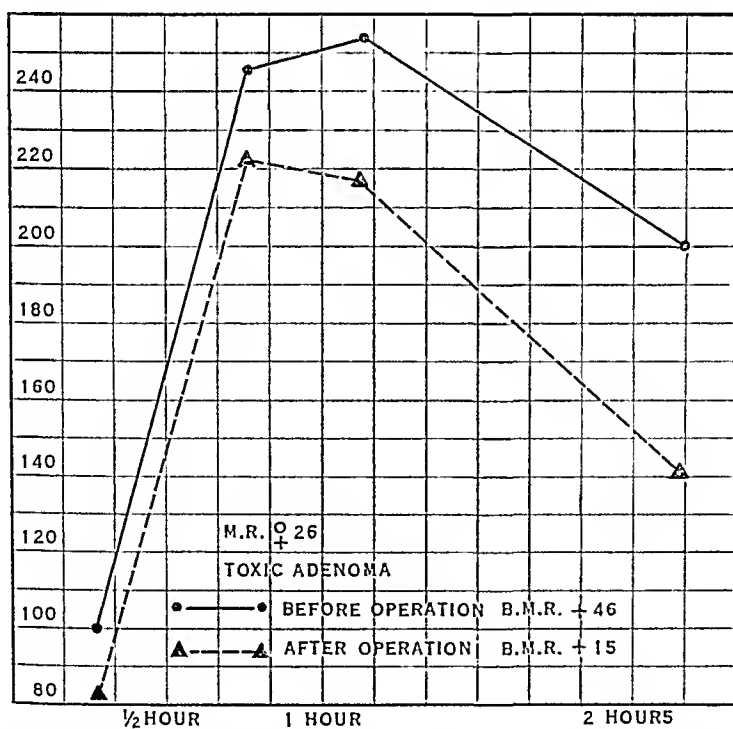


CHART III.—Curve of blood-sugar levels during glucose-tolerance tests before and after thyroidectomy on a patient with toxic adenoma of the thyroid.

secondary hyperglycemia followed injections of glucose or small doses of insulin to rabbits which had been fed thyroid extract, but whose livers still contained glycogen. However, when thyroid extract was fed to the point of depletion of the liver glycogen a small dose of insulin or an injection of glucose produced a fatal hypoglycemia.

The observation of Marks, when coupled with that of Bodansky,<sup>9</sup> is of considerable importance. Bodansky noted that thyroxin administered to sheep caused a rise in the blood sugar. The question naturally arises, from whence does this increase in blood sugar come? If we accept the explanation of Cori, it can come only from the liver. Cori's experiments have proven that muscle glycogen is changed to lactic acid which must be synthesized in the liver to liver glycogen, before it can be mobilized to increase the blood sugar. On the other hand, liver glycogen when mobilized is converted into glucose. Thus the liver is the sole direct source of the blood sugar. It is well known that a hepatectomy causes a fatal hypoglycemia.

These observations, in themselves so pertinent to our theme, are of even greater importance when correlated with those of Denis, Aub and Minot,<sup>10</sup> who found that, although a fasting hyperglycemia was rarely associated with hyperthyroidism, alimentary hyperglycemia was observed in every instance.

It would thus seem that thyroid extract or hyperthyroidism may cause some increase in the blood sugar; that they cause a diminution in the glycogen stores of the liver and, furthermore, the evidence at hand suggests that in hyperthyroidism the liver is not able to store glycogen after feeding as easily as is the normal liver.

We are faced with the fact that even though the liver is glycogen poor, glycogen storage is reduced after feeding. The importance of realizing these facts lies in the relationship which exists between the liver and blood sugar replenishment. Even though the blood sugar may be normal, the liver glycogen supply may be extremely low. As long as the liver contains any available glycogen the blood sugar will be maintained. However, should a crisis demand additional sugar over and above the available supply, hypoglycemia can then readily occur.

One cannot state with any degree of assurance the exact mechanism involved in the hyperglycemic response to the increased secretion of thyroxin. Shpiner<sup>11</sup> believes that the hyperglycemia and glycosuria which follow thyroid feeding are probably due to the increased basal metabolic rate which is associated with thyroid feeding. It is his contention that the thyroid influences carbohydrate metabolism indirectly. Whether the effect is direct or indirect, anyone who has conducted thyroid feeding experiments on the dog will have recognized that the thyroid fed animals are less tolerant to starvation than the control animals.

Abderhalden and Wertheimer<sup>12</sup> reported that thyroxin or thyroid substance administered to dogs, rabbits, guinea pigs, rats and mice caused a reduction in the glycogen content of the animal. This was especially marked in the liver. As the feeding is continued the carbohydrate stored in the liver is totally used up and the blood sugar falls. Associated with these changes, if the feeding is maintained, is a rise in the body temperature, an increase in the carbon dioxid output and death.

One might go on indefinitely reviewing evidence which suggests the very close relationship which the thyroid gland has to carbohydrate metabolism. We are convinced on the basis of the investigations of others and of ourselves that a rational, postoperative therapy must take into consideration this relationship.

For some years glucose has been used in the postoperative period, but not very intelligently. Frequently it was given by rectum, a method we now know to be totally ineffectual. There is no real reason why it cannot be given by mouth, except that one cannot control the rate of absorption. When given intravenously numerous precautions are necessary.

As usually administered intravenously a large amount of glucose has been introduced rapidly into the circulating blood. It is surprising that many surgeons have failed to ascertain the amount of glucose which pours through the kidneys by this method. In 1917 Wilder<sup>13</sup> showed that while the normal individual can take care of 0.8 gm. of glucose per kilogram of body weight per hour when given intravenously, the patient with hyperthyroidism develops glycosuria when as much as 0.6 gm. of glucose per kilogram of body weight per hour is injected. This would indicate faulty glucose assimilation.

Another factor which many investigators and clinicians have not considered as carefully as they should is the state of dehydration which exists in so many of these cases. Dehydration and glycogen content of the liver bear a direct relationship. The liver, even if supplied glucose, will not store it if sufficient fluids are not available. It is of the utmost importance, therefore, to correct dehydration at the same time that an attempt is being made to correct glycogen depletion of the liver. It is much more important to correct dehydration in these cases than it is to correct blood reaction.

For these reasons we are absolutely opposed to the administration of glucose solutions rapidly or in too high concentrations. We have found that a 5 to 10 per cent solution is, as a rule, more satisfactory. Furthermore, we believe that the slow intravenous continuous drop has many advantages over the other methods.

It permits the addition of fluid at a rate at which the tissues, which normally take a part in the storage of water, can accommodate it. Thus other vital cells which normally take little part in water metabolism are not called into action. It lessens the danger of

"speed shock," so that reactions are rare. It permits of the very slow administration of glucose at a controllable rate, so that the injected glucose is utilized both in sparing the body stores and furthermore by supplying additional amounts for storage. It is only rarely that glycosuria appears when glucose is administered in this way. And at the same time it permits one to introduce fluid and food in predetermined amounts, since by regulating the rapidity of the drip one can calculate the total amount of fluid and glucose which can be given in a 24-hour period.

I am convinced that we have less alarming reactions and have saved lives since we adopted this technique. The following records are cited as illustrations of the effect of glucose solution, properly administered, in patients with severe postoperative crises.

**Case Reports.** CASE 1.—D. G., aged 24 years, was admitted to the Thyroid Clinic of the University Hospital, February 12, 1931.

*History.* Her illness covered a period of 18 months, during which time nervousness, emotional instability, tachycardia, tremors, excessive fatigue, frequent headaches and sleeplessness had progressively increased. She had lost 51 pounds in weight. For 3 months she had noticed enlargement of the thyroid and exophthalmos. At that time she was hospitalized elsewhere for 3 weeks, where she was given iodine and kept at rest, with no improvement.

*Previous Medical History.* Pneumonia in childhood; frequent attacks of tonsillitis; tonsillectomy in her twelfth year; appendicitis with appendectomy when 18 years of age.

*Social History.* Married 3 years; deserted by husband after 1 month. One uneventful pregnancy 20 months ago.

*Examination.* Blood pressure was 146 systolic and 70 diastolic. Pulse, 130. Flush over face, neck and thorax. Whole body surface warm and moist. Marked exophthalmos. Diffuse firm thyroid enlargement. Heart action pathologically vigorous. Marked tremor of fingers and tongue. Quadriceps weakness; tendon reflexes hyperactive.

*Electrocardiogram.* Simple tachycardia.

*Basal Metabolism.* In a period of 3 weeks: 82, 60, 54, 63.

*Pre-operative Medication.* Lugol's solution, 15 minims; sodium bromide, 15 gr. luminal,  $1\frac{1}{2}$  daily, from February 13 to March 5, 1931.

*Operation.* March 5, 1931. Right lobectomy. Two hours before she received 0.6 gram of sodium amytal and 15 minutes before morphine sulphate,  $\frac{1}{8}$  gr. and atropine sulphate,  $\frac{1}{16}$  gr. These were supplemented by light nitrous oxide anesthesia. Blood sugar immediately before operation was 76 mg. per 100 cc. and a half hour after operation 104 mg.

Continuous venoclysis glucose, 10 per cent, was started immediately.

8 hours after operation: Temperature,  $102^{\circ}$ ; pulse, 152; respiration, 32.

20 hours after operation: Temperature,  $102^{\circ}$ ; pulse, 160; respiration, 30.

24 hours after operation: Temperature,  $101.3^{\circ}$ ; pulse, 144; respiration, 32; blood sugar, 99 mg.

During the first 24 hours the fluid intake was 2120 cc., including 1500 cc. of 10 per cent glucose. Medication included Lugol's solution, 3 cc.; sodium amytal, 9 gr. and morphine,  $\frac{1}{2}$  gr.

Thirty-two hours: Temperature,  $101^{\circ}$ ; pulse, 184; respiration, 32. Patient delirious. In one of the few moments she was not being watched she got out of bed. Continuous venoclysis resumed.

Forty-eight hours: Temperature,  $101^{\circ}$ ; pulse, 160; respiration, 26.

During the second 24 hours the patient received 2000 cc. of 10 per cent glucose; 1140 cc. water; sodium amytal, 18 gr; Lugol's solution, 4 cc., and morphin sulphate, 1 gr. Venoclysis discontinued.

60 hours: Temperature, 103°; pulse, 148; respiration, 26.  
72 hours: Temperature, 100°; pulse, 128; respiration, 32.  
96 hours: Temperature, 100°; pulse, 104; respiration, 24.  
120 hours: Temperature, 98°; pulse, 100.

**Comment.** This case was recognized as a bad operative risk. Her basal metabolic rates were high and responded only moderately to treatment; she had lost much weight; she had been sick for 1½ years and was not relieved by rest and iodine. It was a matter of no surprise when she developed a crisis marked by great restlessness, delirium and tachycardia. I am reasonably confident, judging from my experience with other cases, that without the continuous glucose venoclysis the patient would not have survived. In this, as in the second case, the tendency to hyperpyrexia seemed to be controlled by the specific glucose therapy.

April 3, 1931. The subsequent convalescence was uneventful. One month after the operation the patient was quite composed, she had gained 3 pounds, was much stronger and had no palpitation.

Once a crisis is established the patient usually succumbs within 48 hours. Only 2 of our cases have lived beyond that time.

**CASE 2:**—M. S., aged 30 years, was admitted to the Thyroid Clinic of the University Hospital, January 12, 1931.

*History.* For 2½ years she had suffered with nervousness, weakness, palpitation, dyspnea, emotional instability and exophthalmos. She had lost 32 pounds. Five weeks after the onset of her illness she had a thyroid operation elsewhere. Her goiter was not reduced in size and all of the signs and symptoms of thyrotoxicosis were aggravated, becoming progressively worse until admission.

*Past Medical History.* Quinsy 9 years ago followed by tonsillectomy.

*Family History and Social History.* Inconsequential.

*Examination.* Blood pressure was 200 systolic and 110 diastolic; pulse, 130.

Marked exophthalmos, very restless, face flushed, skin warm and moist. Marked bilateral thyroid enlargement. Heart enlarged; systolic apical murmur. Marked tremors of fingers and quadriceps weakness.

White blood cells, 9600. Fractional gastric analysis showed no free hydrochloric acid.

*Basal Metabolism.* Before operation: 47, 32, 30.

*Pre-operative Treatment.* Lugol's solution, 16 minims; sodium bromid, 1 gram luminal, 1½ gr. daily for 19 days.

*Operation.* January 31, 1931. Avertin, 5.2 cc., was given 1 hour before a right lobectomy under light nitrous oxid anesthesia. The pulse was 148 at the start and 120 at the end of the operation. At no time was there free bleeding. When she arrived at the ward the blood pressure was 162 systolic and 98 diastolic; temperature, 98°; pulse, 152; respiration, 32.

Twelve hours after the operation the temperature rose to 102.3° and the pulse to 192. At the time I did not anticipate she would survive more than a few hours. She was given 400 cc. of 5 per cent glucose, and her condition improved almost immediately. The crisis seemed under control.

Twenty-four hours after the operation a second crisis seemed impending.

The temperature which had returned to normal rose to 101° and the pulse to 186. She became cyanotic and again the end seemed not far off. Continuous intravenous medication with 5 per cent glucose was begun. In the second 24 hours she received 3500 cc. of a 5 per cent glucose and again there followed a degree of improvement which encouraged us to believe the crisis had been stemmed.

Unfortunately at this time it was evident the patient was developing pneumonia to which she eventually succumbed, but not until 86 hours after the operation. The necropsy revealed a status thymolymphaticus, bilateral bronchopneumonia and a right lobar pneumonia.

**Comment.** It is my belief that had the patient not developed pneumonia she would have survived. At all events she did not succumb within the first 48 hours as did most other patients in crisis, but lived 3½ days. I am inclined to believe her life was prolonged by the liberal use of glucose.

Just what causes these crises is as yet a matter of speculation. That glucose helps to tide the patient over a very critical period we feel sure. Perhaps the entire process is one of disturbed carbohydrate metabolism, though the problem may be more complicated. Perhaps it is also associated with an acute thyroid or parathyroid dysfunction or both over which glucose may have a moderating influence. I realize we have been delving in matters controversial, but if progress is to be made we must permit ourselves to indulge in speculation. In some particulars we have gone beyond the speculative field as to carbohydrate metabolism and as to the relation of the thyroid to pancreas and liver.

**Summary.** 1. There is both experimental and clinical evidence to prove that hyperglycemia is associated with hyperthyroidism.

2. Hypertrophy of the islands of Langerhans has followed thyroidectomy and *per contra* in exophthalmic goiter with glycosuria there is a decrease in these islands.

3. Hyperthyroidism exhausts the glycogen stores in the liver, the liver seems to be the only source of blood sugar.

4. A crisis may demand sugar over and above the available supply and may precipitate a fatal hypoglycemia.

5. If we recognize a relationship between thyroid dysfunction and carbohydrate metabolism, glucose properly administered may be a rational agent in the management of postoperative crises.

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## THE EFFECT OF EPHEDRIN UPON THE HUMAN STOMACH AS DETERMINED ROENTGENOLOGICALLY.

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Few roentgenologic observations concerning the effect of ephedrin upon the human stomach\* have been made. These reports are conflicting.

Pollak and Robitschek (1926),<sup>1</sup> using the roentgenologic method, noted that gastric peristalsis and the rate of gastric emptying were increased after oral ingestion (20 drops of 10 per cent solution), but were unable to venture an opinion whether this was due to a direct stimulation of the gastric musculature or a reflex action as a result of the irritant effects on the mucosa. Marcou and Savulesco (1928)<sup>2</sup> worked with this same problem, employing a different method. Ephedrin was injected intravenously in varying amounts after the subject swallowed a balloon which was connected with a water manometer. Doses of 0.1 to 20 mg. produced an inhibition of gastric movements, followed by exaggerated movements in the case of the 20-mg. dose. Doses below 0.1 mg. either produced no effect or transitory contraction only. Scholtz and Mohos (1929)<sup>3</sup> studied 22 cases roentgenologically, examining each case routinely without the drug for control purposes and repeating the test with the drug (0.05 gm. subcutaneously) on the following day. They

\*Throughout this study the duodenal bulb and stomach have been considered as a single functional or physiologic unit, and the expression, stomach, should be interpreted by the reader as having this connotation.



found a constant inhibiting effect on tone and peristalsis, with prolongation of emptying time.

Thus a considerable difference in opinion arises. These opinions vary from a purely stimulative effect to one of pure inhibition.

Several attempts have been made to solve this problem by studying the action of ephedrin experimentally on animals, but here also much of the evidence is conflicting. This is particularly true of the isolated muscle preparation. With the organ *in situ*, few observations have been made. These, in general, suggest a relaxation with inhibition of peristalsis (Kinnaman and Plant, 1927<sup>4</sup>; M'Crea and MacDonald, 1928<sup>5</sup>). Chen and Schmidt (1930)<sup>6</sup>, after an excellent summary of these effects, write the opinion: "So it is very evident that the effects of ephedrin upon movements of the gastrointestinal tract *in situ* appear to be much more nearly like those of epinephrin than in the case when two agents are tested upon isolated muscle preparations." As Chen and Schmidt add, it is the effects obtained with the organ *in situ* which are of therapeutic or clinical importance. It was believed by the present writer that roentgenologic observations were valuable in a study of this type because it permitted the study of the effects with the organ *in situ* without the introduction of abnormal stimuli incident either to operation or anesthesia.

Antispasmodics have long been used by the roentgenologist in his gastrointestinal work. Atropin has been used chiefly in this respect, and by many was believed to possess diagnostic significance in the differentiation of functional or reflex spasm from that due to an intrinsic lesion. More recently, Holmes and Dresser (1928)<sup>7</sup> have used amyl nitrite to relax spasm. Its action was found to be irregular, particularly in cases of pylorospasm. Ephedrin, though now a well-known antispasmodic, has not been used by roentgenologists in studying the gastrointestinal tract.

The present study was undertaken to: (a) Determine the effect of ephedrin on tone, peristalsis and spasm of the stomach; (b) study its effects comparatively in stomachs with and without local disease; (c) compare its objective effects with atropin. The physiologic action of atropin is produced, of course, in an entirely different way than in the case of ephedrin, the former producing relaxation through the inhibition of the parasympathetic while ephedrin appears essentially sympathicomimetic (Chen and Schmidt, 1930<sup>6</sup>).

**Method.** Fifty-eight cases were studied before and after the oral administration of ephedrin and 39 cases before and after the subcutaneous injection of atropin. The repeat examination with ephedrin or atropin was always made on the same day and within 0.5 hour after the first examination. This was considered a necessary prerequisite, since normal stomachs vary markedly from day to day in tone and peristalsis and in the presence or absence of spasm. The failure to take this time factor into account will result

in faulty deductions concerning the influence of any drug upon the stomach and is an objection to the study of the effects of atropin after oral administration, since considerable time must elapse before an individual can be safely atropinized by the oral method. Many types of spasm are transitory, and the disappearance of spasm on a second examination should not be taken as evidence that any drug administered between the two examinations produced the effect observed, if a considerable time elapses between the first and second examinations.

Ephedrin possesses this great advantage, that the physiologic effect of the drug is obtained within a matter of minutes after oral ingestion. Usually 30 minutes were sufficient, though many of the cases were followed longer (1 to 2 hours) in order to make several sets of observations on the same case. The dose of ephedrin varied from 50 to 150 mg. The drug was the natural product of Ma Huang manufactured by Eli Lilly & Company and by the Abbott Laboratories. While there are 6 isomers of ephedrin, and the intensity of the physiologic effects vary according to the isomers used, only 2 of these (l-ephedrin and d-pseudoephedrin) occur in the natural product (Chen, Wu and Henriksen, 1929<sup>8</sup>). Both of these are known to exert a pressor effect (cats), the former showing the more pronounced effect. Both are reported by Chen and his associates to have an inhibiting effect on the smooth muscle of the intestines of the rabbit. The natural product, therefore, would appear to be satisfactory for a study of this type; in fact, many of the artificially prepared isomers would probably not be as satisfactory if the pressor effect be accepted as a reliable guide. The natural drug is mostly l-ephedrin, and this is known to be very active, physiologically exerting a pressor effect approximately 35 times as great as the weakest isomer.

In order to insure the employment of an adequate physiologic dose, blood pressure and pulse rate were taken before and after the administration of ephedrin, with the patient recumbent. If neither of these were affected by the drug the dose was repeated until the pressor effect was obtained. An increase in blood pressure or pulse rate of 15 was the smallest elevation accepted as indicative of the pressor or the cardiac stimulant effect.

The cases were selected during the course of routine gastrointestinal examinations usually because of the presence of spasm, though in many instances spasm was absent, and the drug was administered to determine the effect on peristalsis and tone. A total of 97 cases were studied, of which 58 were given ephedrin and 39 atropin. The subjects were all adults, varying in age from 20 to 73 years.

**Results.** *Action of Ephedrin on Tone, Peristalsis and Spasm of Normal Stomachs Free of Organic Disease.* Out of the total of 58 cases studied 32 cases were found to be free of local disease.

Thirteen of these were studied with particular attention to peristalsis and tone. In 11 cases peristalsis was definitely decreased, while in 2 no demonstrable change was apparent. In all cases where peristalsis was diminished the tone was likewise decreased. Figs. 1 and 2 show the usual reaction obtained in normal stomachs.

Twenty-one of the 32 cases were studied because of the presence of spasm. Most of these were cases of pylorospasm, though 5 of them showed spasm at a distance from the pylorus affecting the pars media. After ephedrin, 10 out of 15 cases of pylorospasm showed a disappearance of the spasm sufficient in degree to permit the filling of the duodenal cap. In most of these cases, however, the relaxation was not complete and barium passed only in small amounts from the pylorus. The remaining 5 out of 15 cases showed no change, and in several of the cases the spasm appeared to be greater than at the initial examination. Figs. 3 and 4 illustrate the persistence of pylorospasm of the stomach in a young adult (without evidence of a local lesion) after a dose of 150 mg. of ephedrin. This patient showed a very marked pressor effect, but in spite of the fact that the dosage was sufficiently high to produce a decided physiologic reaction, the spasm did not disappear. Of the 5 cases showing spasm elsewhere in the stomach, 4 showed a notable change with practically complete disappearance of spasm.

A typical case of advanced cardiospasm was examined during this series and carefully followed after ephedrinization. The ephedrin exerted no observable effect on the spasm of the esophagus, though the ephedrin effect on the stomach (diminished peristalsis and tone) was evident.

Thus, in summary it is to be noted that ephedrin commonly decreases tone and peristalsis of the normal stomach or of the stomach free of organic disease. In this series there was no evidence of a stimulating effect either in tone or peristalsis. Ephedrin, on the other hand, does not appear to be as effective in relaxing pylorospasm, though in many cases (two-thirds) a partial effect is obtained. In a single case of cardiospasm no effect on the spasm was apparent.

*Action of Ephedrin on Tone, Peristalsis and Spasm in Cases of Organic Disease.* The chief intrinsic lesion (lesion within upper gastrointestinal tract) in these cases was duodenal ulcer (14 cases); a few cases of extrinsic lesions, such as periduodenal adhesions (7 cases), cancer of gall bladder (1 case) and cancer of esophagus (1 case) are included. Three cases were of undetermined origin. Eleven of the 14 cases of duodenal ulcer were studied with particular attention to changes in peristalsis and tone. In 6 of these there was evidence of a decrease in peristalsis and tone, the others showing no perceptible effect. Seven cases of duodenal ulcer showed persistent spasm, chiefly pylorospasm, and in only 2 of these cases was any change noted after ephedrin. A typical incisura of the duodenal cap due to the presence of a local ulcer was followed in this

group. Figs. 5 and 6 illustrate the persistence of the spasm of the circular muscle fibers at the level of the ulcer after a dose of 125 mg. of ephedrin.

TABLE 1.—RESULTS OBTAINED ON TONE, PERISTALSIS AND SPASM AFTER THE USE OF EPHEDRIN.

Type of lesion.	Effect on tone and peristalsis.			Type of spasm.	Effect on spasm.		
	No. of cases.	Relax. prod.	No change.		No. of cases.	Relax. prod.	No change.
No lesion, 32 cases	13	11	2	Cardiospasm	1	0	1
				Pylorospasm	15	10*	5
				Other spasm	5	4	1
Local lesions: duodenal ulcer, 14 cases	11	6	5	Cardiospasm	0		
				Pylorospasm	6	2	4
				Other spasm	1	0	1
Extrinsic lesions, 9 cases	3	3	0	Cardiospasm	0		
				Pylorospasm	5	1	4
				Other spasm	1	0	1
Undetermined, 3 cases.	1	0	1	Cardiospasm	0		
				Pylorospasm	1	0	1
				Other spasm	1	1	0
Totals, 58 cases	28	20	8	....	36	18	18

\* Partial.

The extrinsic lesions (9 cases) were similarly studied. Three were followed for changes in tone and peristalsis, with a positive result in all 3. Five cases of pylorospasm were followed in this group and in only 1 case was any change apparent. A typical incisura of the stomach was followed in this group and ephedrin was without effect.

Summarizing, relaxation after ephedrin in the presence of a local intrinsic lesion occurs in about one-half of the cases. This is considerably less than noted in cases in which the stomach and bulb show no lesion. It is probable, however, that the use of ephedrin possesses no diagnostic value in the differentiation of intrinsic and extrinsic lesions, though the high tone and spasm tend to persist longer and are modified less by ephedrin in cases where local disease is present.

Blood-pressure readings and pulse rates were recorded on approximately two-thirds of the cases in order to insure giving the drug in adequate doses. These were of interest in showing that usually either blood pressure became elevated or the pulse rate increased, but it was uncommon for both the blood pressure and pulse rate to increase markedly (above 15 points) in the same subject. Only 5 cases in this series showed both an elevation of blood pressure and heart rate exceeding 15. In fact, in several of the cases the pulse was actually slowed while the blood pressure became elevated.

This slowing of the pulse is probably compensatory to the pressor effect.

Pronounced reactions to the drug at the dosages given were distinctly uncommon. Evidence of slight toxic effects was found in approximately 15 per cent of the cases. These effects consisted chiefly of nausea and palpitation. In some of the cases direct questioning was required to elicit information concerning these reactions. While nausea was one of the common slight reactions, vomiting occurred in only 1 case. Two cases showed a transitory arrhythmia. In general, reactions were absent or minimal in those cases where the pressor effect of the drug was not marked. In only 1 case was a violent reaction obtained. This occurred in a nervous young Italian, of rather slender build. His blood pressure rose from 122 systolic, 80 diastolic to 205 systolic, 110 diastolic at the end of the first hour, reaching a peak of 220 systolic, 115 diastolic at the end of the second hour. Marked nausea and a severe pounding headache, the throbbing character of which made the patient aware of each cardiac systole, were the outstanding features. There was some retching, but only a few cubic centimeters of bile-stained material were vomited. His blood pressure fell during the course of the third hour and reached a level of 165 systolic, 90 diastolic at the end of 2.75 hours, and as it fell the reaction diminished. His pressure on the following morning was normal (120 systolic, 78 diastolic). This patient was given the drug because of the presence of pylorospasm, and it is a noteworthy fact that the drug not only failed to remove the spasm, but the reaction appeared to make the spasm more pronounced, the latter affecting the duodenal cap as well as the pyloric end of the stomach. (Fig. 4.)

**Atropin Series.** In the following series 39 individuals were examined prior to the injection of 1.5 mg. of atropin subcutaneously, and after the lapse of approximately 25 to 30 minutes were re-examined to observe changes. The subcutaneous route was employed in order to avoid, as much as possible, the time factor. In order to insure employing atropin in proper physiologic dosage the pulse rate and dryness of mouth were followed. All cases at the time of the second examination showed definite dryness of the mouth and usually an increase of 20 to 30 in pulse rate. Exceptionally an increase of 40 or more occurred.

*Action of Atropin in Cases Showing No Local Lesion.* Twenty, or approximately one-half, fell in this group. Five cases of markedly active peristalsis were followed, and in 4, after atropin, peristalsis and tone were much diminished. In 8 cases of pylorospasm relaxation of spasm was noted in only 3. Five cases of cardiospasm were followed without noting any effect. Seven cases of spasm of stomach proper showed a definite change in only 3. That atropin may fail to relax spasm of a reflex character in the absence of any local lesion is well shown by the detailed study of a case of



FIG. 1. Before ephedrin.

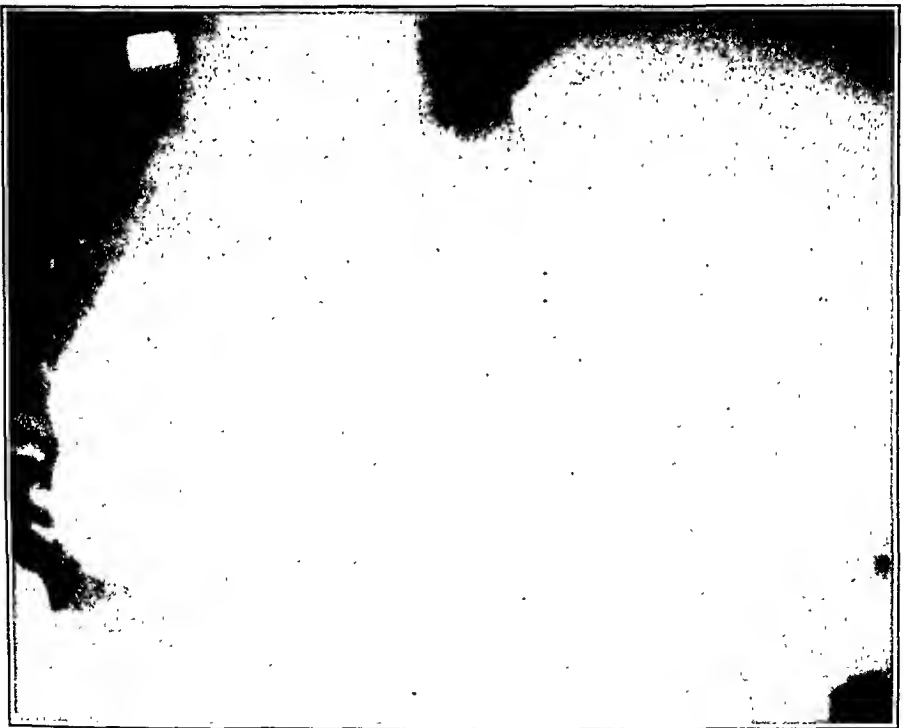


FIG. 2.—After ephedrin.

FILMS OBTAINED BEFORE AND AFTER EPHEDRIN ILLUSTRATING THE USUAL RELAXATION OBTAINED BY THE DRUG IN THE NORMAL STOMACH.

H. M., aged 38 years, male, entered with a complaint of lower abdominal pain of 4 years duration not related to meals. Physical examination was negative except for a few carious teeth. The gastrointestinal series showed a normal stomach and duodenum. Twenty minutes after 100 mg. of ephedrin orally, the tone of the stomach diminished. Note, however, that faint waves of peristalsis can be identified over the lower end of the stomach. It was a common finding to note that in the normal stomach peristalsis was commonly diminished rather than completely abolished.



FIG. 3.—Before ephedrin.



FIG. 4.—After ephedrin.

#### CASE OF PYLOROSPASM NOT RELIEVED BY EPHEDRIN.

E. N., male adult, aged 38 years, gave a history of vague distress after meals, varying in time but commonly immediately after eating. The physical examination was essentially negative. The gastrointestinal series showed no evidence of a local lesion. There was persistent spasm affecting the pyloric end of the stomach. A large oral dose of 125 mg. failed to relax this spasm though the drug produced a marked pressor effect (elevation of systolic pressure of 100). Note that the contraction of the lower stomach appears more marked after the ephedrin and that the base of the cap has become similarly affected.

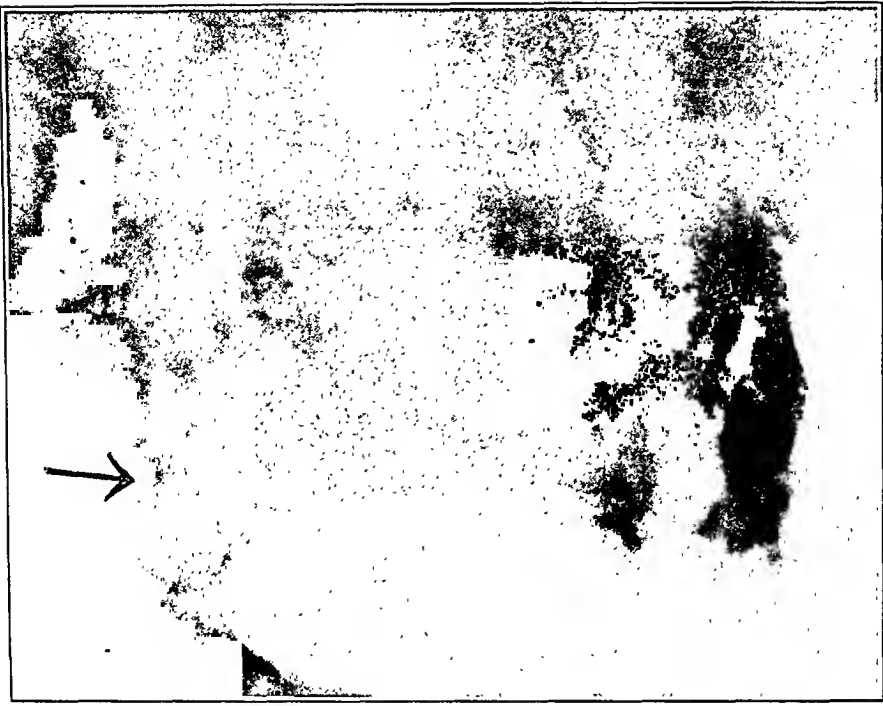


FIG. 5.—Before ephedrin.

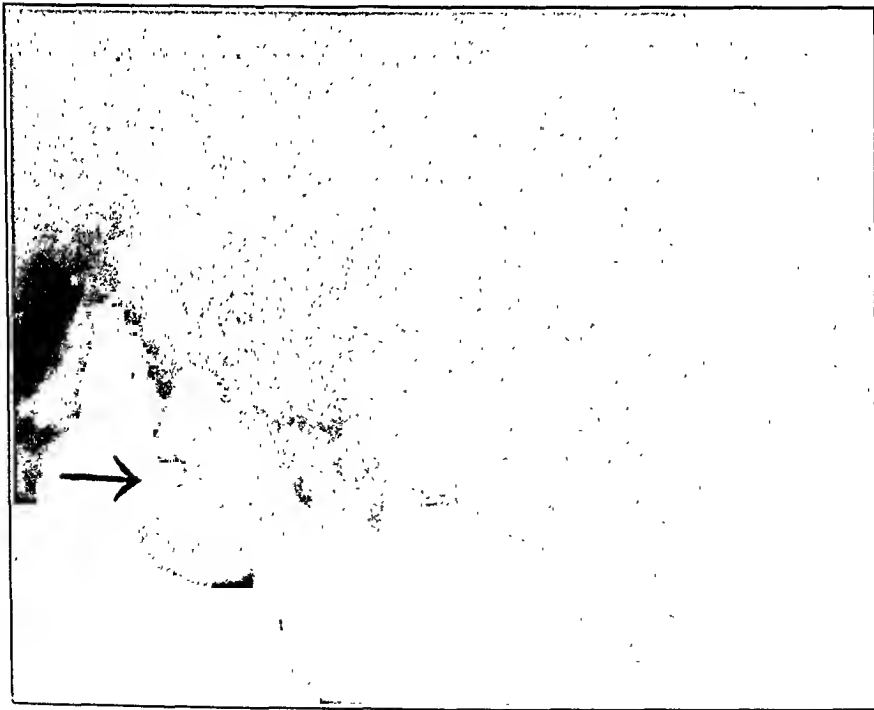


FIG. 6.—After ephedrin.

ILLUSTRATING THE PERSISTENCE OF THE INCISURA OF DUODENAL ULCER AFTER  
EPHEDRINIZATION.

J. S., male, aged 52 years, gave a twenty-year history of postprandial distress relieved by food and soda. Gastrointestinal examination showed a persistent deformity of the lesser curvature with a spastic incisura of the greater curvature of the cap. Ephedrin sulphate (125 mg. orally) failed to relax the spasm of the cap. The patient died with cerebral hemorrhage one week later. At autopsy the diagnosis of duodenal ulcer was verified.



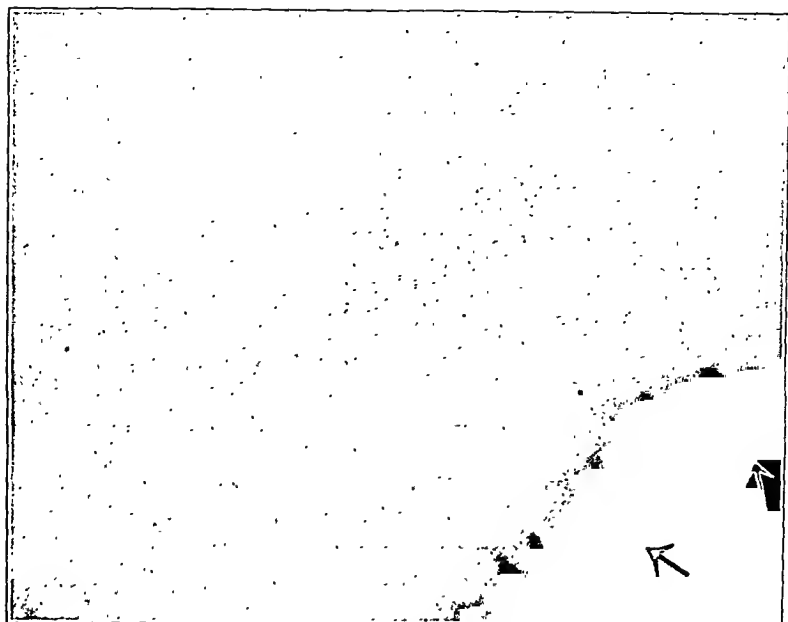


FIG. 7.—Before atropin.

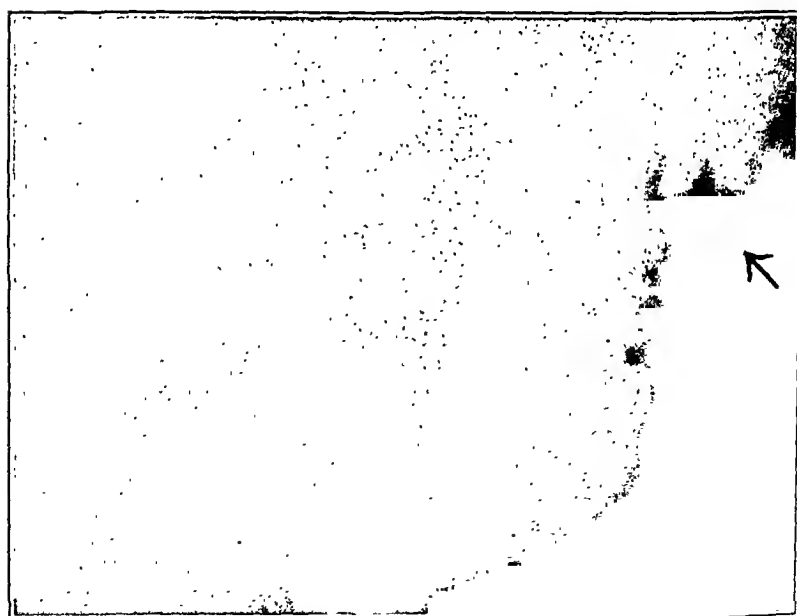


FIG. 8.—After atropin.

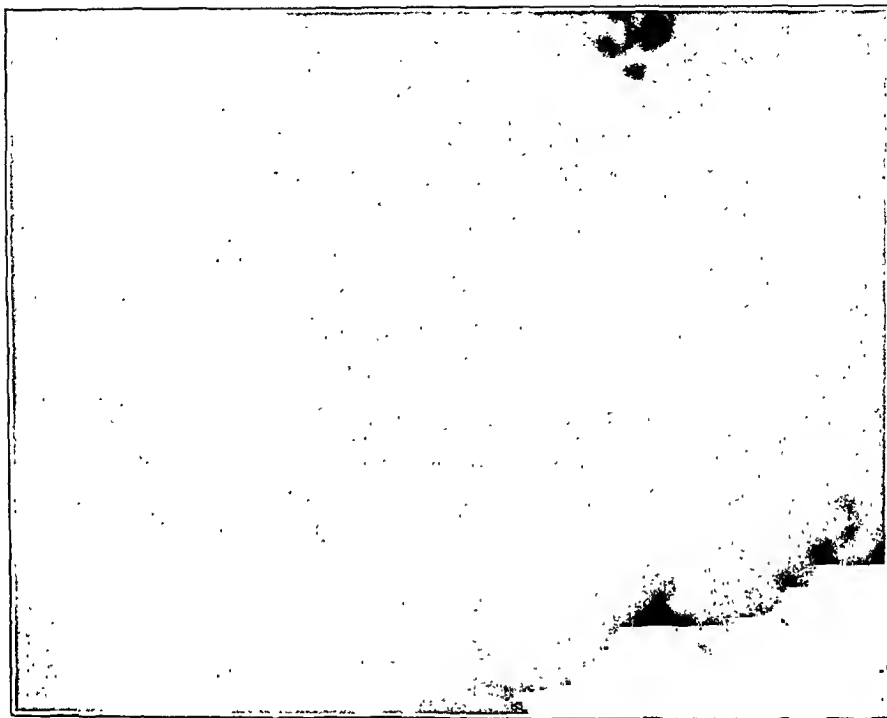


FIG. 9.—Following day.

ILLUSTRATING FAILURE OF ATROPIN TO RELAX REFLEX SPASM.

E. R., adult male, aged 47 years, gives long history of drug addiction and of syphilis of the central nervous system. He was examined roentgenologically because of history of spells of nausea and vomiting, only relieved by morphin. Gastric examination made without motility studies at a time when the patient was experiencing an attack showed a large defect on the greater curvature over which no peristalsis passed and which persisted after atropin (1.5 mg.), subcutaneously. Large doses of morphin gave only symptomatic relief. An examination on the following day revealed an entirely normal stomach with the defect absent and with normal peristalsis passing over this area. He was operated upon one week later. At this time an essentially normal stomach was found.

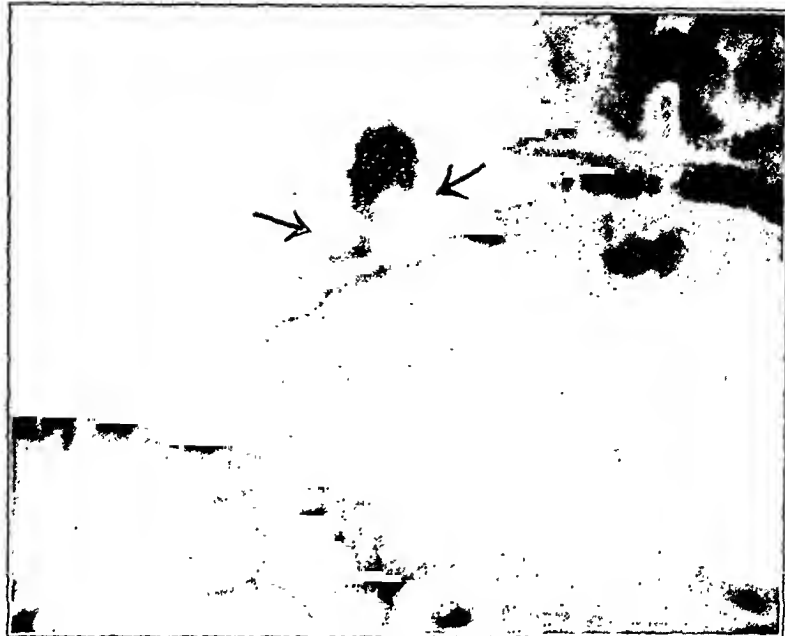


FIG. 10.—Before atropin.

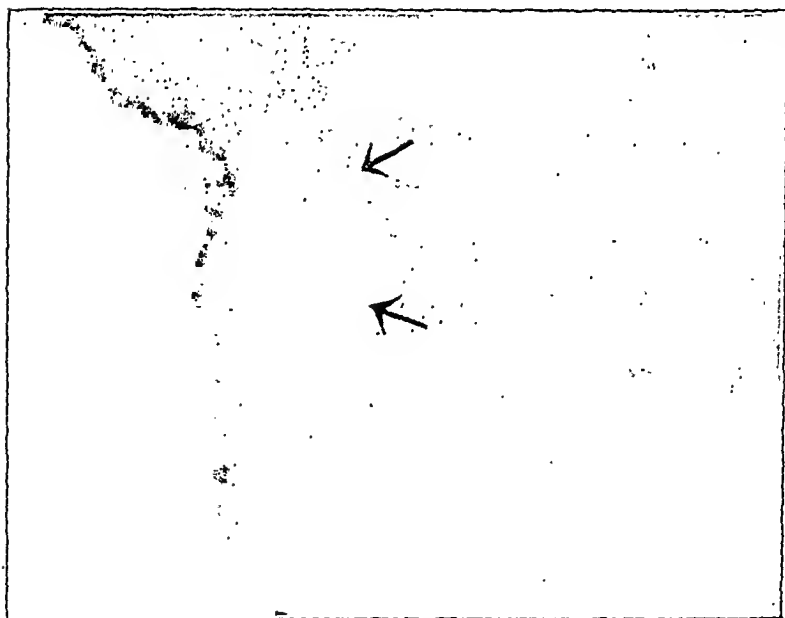


FIG. 11.—After atropin.

ILLUSTRATING FAILURE OF ATROPIN TO RELAX SPASM RELATED TO AN EXTRINSIC LESION.

(Chronic Cholecystitis with Cholelithiasis).

C. B., an adult male, aged 41 years, gave a history of lower abdominal pain of 2 years duration. At the gastrointestinal examination a persistently irregular, spastic cap was noted. After 1.5 mg. of atropin subcutaneously, the cap was followed carefully, fluoroscopically and by films. Large, irregular defects persisted in the cap. Peristalsis of the stomach was not affected. Three days after the gastrointestinal examination, a gall bladder with thickened walls and with 236 faceted stones varying in size from 0.5 to 1.5 cm. in diameter was removed at operation. The stomach and duodenum showed no evidence of pathology.

gastrosplasm occurring in a patient addicted to the use of morphin, with cerebrospinal lues. (Figs. 7, 8 and 9.) This case was examined both before atropin and after atropin and later after morphin. Neither of these two drugs produced any observable result, though the morphin relieved the pain of which the patient was complaining. That this defect was entirely spastic was proved by observations on the following day, when an entirely normal gastric contour was outlined, and by subsequent operation when no pathology relating to the stomach was found.

TABLE 2.—RESULTS OBTAINED ON TONE, PERISTALSIS AND SPASM AFTER THE USE OF ATROPIN.

Type of lesion.	Effect on tone and peristalsis.			Type of spasm.	Effect on spasm.		
	No. of cases.	Relax. prod.	No change.		No. of cases.	Relax. prod.	No change.
No lesion, 20 cases . .	5	4	1	Cardiospasm	5	0	5
Local lesions: duodenal ulcer, 12 cases; gastric carcinoma, 2 cases; gastric ulcer, 1 case .	8	5	3	Pylorospasm	8	3	5
				Other spasm	7	3	4
				Cardiospasm	0		
				Pylorospasm	10	2	8
				Other spasm	5	1	4
Extrinsic lesions, 4 cases	4	1	3	Pylorospasm	1	1	0
				Other spasm	1	0	1
Totals, 39 cases . .	17	10	7	....	37	10	27

*Action of Atropin in Cases With Local Lesion.* Twelve cases of duodenal ulcer were studied and 8 of these showed marked hyperperistalsis affording us a good opportunity to follow this effect. Five out of 8 showed notable diminution of peristalsis and tone. The remaining 3 were unaffected, although atropin had been given in physiologic dosage. A case of gastric carcinoma likewise showed no change. Ten cases of duodenal ulcer were selected because of the presence of pylorospasm, and in only 2 cases was a definite positive result achieved. Two cases of duodenal ulcer showed reflex spasm of the stomach which was not affected by atropin. A single case of gastric ulcer showed marked spasm which was unaffected. Similarly,<sup>2</sup> cases of gastric cancer associated with spasm showed no change after atropinization. Four cases of extrinsic pathology (duodenal adhesions, cholelithiasis and extrinsic mass) were studied. Diminution of peristalsis was noted in only 1. The failure of atropin to relax duodenal spasm in a case of extrinsic pathology (cholecystitis with cholelithiasis) is well illustrated by Figs. 10 and 11. This patient showed unusually deep spasm which greatly deformed the cap, simulating an ulcer. Atropin did not remove this spasm, though operation a few days later proved the

diagnosis of cholelithiasis and demonstrated the absence of pathology in the duodenum.

**Summary.** Ephedrin accomplishes much the same objective result that is seen after atropinization. Peristalsis and tone became decreased in the vast majority of individuals with normal stomachs after either ephedrinization or atropinization while these effects occur much less frequently if a local lesion is present. While ephedrin was as successful as atropin in this series in relaxing spasm, attention is called to the obvious finding that both of these drugs failed to relax spasm in one-half or more of the cases studied. No case of cardiospasm appeared benefited by either drug, and in cases of pylorospasm it was a common finding to note only partial relaxation. Neither of these two drugs should be accepted as a diagnostic agent in the differentiation of an intrinsic lesion from an extrinsic one with reflex spasm. Both of these drugs relax spasm in the presence of local disease, and it was a very common finding to note the absence of any relaxation after the use of these drugs in stomachs which were obviously entirely normal.

It is quite probable that the impression of the usefulness of atropin in this regard has been gained because at a second examination on a succeeding day cases in which no intrinsic local lesion was present did not show spasm, while spasm persisted in cases that had local lesions. This undoubtedly is true, but this present work would indicate that this is due to the time factor rather than any constant action of the drug. It is rare for a normal stomach, free of local lesions, to show the same spasm at the same level on different days.

**Conclusions.** 1. Ephedrin commonly produces a diminution in peristalsis and tone in the human stomach free of local disease.

2. In relaxing spasm the action of ephedrin is more variable, often failing in cases of pylorospasm in stomachs free of local pathology.

3. In stomachs showing local disease spasm is less often affected by ephedrin and less modified when affected than in normal stomachs.

4. Ephedrin accomplishes much the same objective result that is seen after atropinization, though its mode of physiologic action is different.

5. Neither ephedrin nor atropin should be accepted as a specific diagnostic agent in the differentiation of an intrinsic lesion from an extrinsic one.

6. Both of these drugs may relax spasm in the presence of local organic disease or may fail to relax spasm of a reflex or functional character.

7. If it is desired to relax a stomach in order to study a questionable deformity more readily ephedrinization has the obvious advantage over the use of atropin in that the former can be accomplished in a few minutes by the oral method, permitting the entire study to be finished at one examination.

8. Great emphasis is placed, however, on the value of a second examination on a succeeding day in the study of spasm, since stomachs free of organic pathology rarely show the same spasm at a second examination.

9. These drugs are not effective in the relaxation of cardiospasm, and their action in cases of pylorospasm is variable.\*

\* I desire to express my thanks to Dr. S. L. Warren for aid in preparing the manuscript.

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## A STUDY OF THE FIVE-HOUR DEXTROSE TOLERANCE CURVE IN TREATED DIABETIC PATIENTS.

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THE severity of diabetes has often been measured by the degree of hyperglycemia that followed the ingestion of a given amount of glucose. The majority of investigators have confined themselves to a study of the blood sugar curve over a period of 3 hours, although it is generally felt that the persistence of such a hyperglycemia is of more significance than the height.<sup>1,2,3,4,5,6</sup> John<sup>2</sup> thinks the most significant abnormal feature of such a curve may be its failure

to return to the normal fasting level in 3 hours. He considers the absolute height of relative value. Mosenthal<sup>5</sup> also stresses the importance of duration of the hyperglycemia. MacLean and DeWesselow<sup>6</sup> interpret the ability to get rid of the increased blood sugar and return to a normal value within a limited time after sugar ingestion, as the best indication of an effective carbohydrate metabolism. Some investigators only consider a curve that is abnormal for 3 hours diagnostic of diabetes.<sup>3,9</sup> Ohler<sup>10</sup> has wisely stressed the importance of keeping the mild cases under observation. Rabinowitch,<sup>7</sup> who observed the relation of the respiratory quotient and blood sugar following glucose, feels that "the presence of a normal blood sugar 3 hours after glucose ingestion is not a sufficient basis for the diagnosis of a normal carbohydrate metabolism." He found the rate of utilization of glucose in diabetics much below that of the average normal individual, although no perfect correlation existed between this rate and the severity of the disease.

Because of these facts we decided to study the curve over a longer period of time, and to observe the relation of the height of the hyperglycemia to its duration and of these two to the severity of the diabetes. A period of 5 hours was selected, as this is the average interval between meals for most adults. A total of 26 cases was studied. This included 5 normals, 6 mild diabetics, 1 renal glycosuria, 6 moderately severe and 8 severe diabetics. All of the diabetics were patients who were being treated in the Diabetic Clinics of the University and Bellevue Hospital Medical College of New York University, so that the diet, general condition and progress of the patient were observed both before and after the tolerance test. The diet at the time the observations were made was a continuation of the one the patient had been taking, and had been uniform for a period of at least 3 weeks. The carbohydrate, protein and fat values are recorded in the tables. Sweeney<sup>8</sup> has shown that the character of the blood sugar curve in normal individuals can be greatly influenced by the previous carbohydrate, protein or fat content of the diets. When the pancreas had been stimulated by a high carbohydrate diet the carbohydrate mechanism responded more quickly and the hyperglycemia was prevented. The cases on a high fat diet showed a marked decrease in tolerance. A high protein diet caused a mild inability to utilize glucose. None of the patients in our series was on a high fat diet and all but 1 patient received more than 105 gm. of carbohydrate daily.

**Procedure.** Patients who had run mild, moderate or severe clinical courses were selected for the observations. An effort was made to obtain an equal number of each type. The criteria for these groups based on clinical observations were: (a) The starving blood sugars taken during the patient's attendance at the clinic; (b) the carbohydrate content of the diet; (c) the patient's ability to remain sugar free on the diet; (d) the amount of insulin required to

TABLE 1.—MILD DIABETICS.

Case No.	Blood sugar, mg. per 100 cc.							Greatest rise in mg. of bld. sug.	Period of hyperglycemia, hours.	Urine sugar, gm.	Diet at time of curve.				Daily insulin, units.	Present diet.			Age.	Duration of diabetes.
	Number of hours after taking 100 gm. glucose.										Carb., gm.	Prot., gm.	Fat, gm.	Carb., gm.		Prot., gm.	Fat, gm.			
	Starv.	0.5.	1.	2.	3.	4.	5.													
6.	87.3	108.0	160.0	122.7	108.1	64.7	50.7	81.0	2	3.0	Moderate starch	0	Same		0	Controlled starch	46	Indefinite.		
7.	94.6	90.9	129.8	188.7	125.0	82.0	77.0	98.0	3	10.3	117 53	0	Controlled starch		0	Controlled starch	34	7 yrs.		
8.	92.0	181.0	205.0	137.0	103.0	90.0	88.0	113.0	2	0.4	130 50	0	Controlled starch		0	Controlled starch	40	Indefinite.		
9.	109.0	156.0	198.0	173.0	131.0	128.0	113.0	91.0	4	Tr.	116 56	0	140 60		0	102	61	5 yrs.		
10.	86.9	121.9	134.2	128.2	81.3	80.2	82.0	103.6	2	Tr.	50 45	0	Controlled starch		0	Controlled starch	68	Indefinite.		
13.	95.2	333.0	190.5	125.0	85.5	80.9	64.7	237.8	2	Tr.	150 62	0	Controlled starch		0	Controlled starch	50	1.5 yrs.		

\* Blood sugar at 1.5-hour period.

TABLE 2.—MODERATELY SEVERE DIABETICS.

Case No.	Blood sugar, mg. per 100 cc.							Greatest rise in mg. of bld. sug.	Period of hyperglycemia, hours.	Urine sugar, gm.	Diet at time of curve.			Daily insulin, units.	Present diet.		Age.	Duration of diabetes.	
	Number of hours after taking 100 gm. glucose.										Carb., gm.	Prot., gm.	Fat, gm.						
	Starv.	0.5.	1.	2.	3.	4.	5.												
11 . . .	93.5	172.0	235.0	254.0	186.0	102.0	78.4	160.5	3	5.5	112	62	120	5	112	62	120	69	?
12 . . .	90.0	145.3	200.0	200.4	222.0	181.8	120.9	132.0	4	4.5	112	62	120	0	Not returned			52	?
14 . . .	109.0	235.3	253.2	250.0	274.0	183.5	137.9	165.0	4	8.7	112	62	120	10	112	62	120	39	1 yr.
15 . . .	125.0	307.5	210.0	222.0	153.0	117.8	80.0	182.5	3	2.6	105	55	101	0	105	55	101	59	5 yrs.
16 . . .	148.0	153.8	285.6	350.8	250.7	166.7	121.0	201.0	4	11.0	115	56	102	0	160	58	104	63	5 yrs.
25 . . .	125.0	178.6	241.0	173.9	150.0	111.0	74.1	116.0	3	Tr.	112	55	106	0	142	57	95	50	1 yr.

TABLE 3.—SEVERE DIABETICS.

Case No.	Blood sugar, mg. per 100 cc.							Greatest rise in hyperglycemia, mg. of bld. sug.	Period of hyperglycemia, hours.	Urine sugar, gm.	Diet at time of curve.			Daily insulin, units.	Present diet.			Age.	Duration of diabetes, yrs.
	Number of hours after taking 100 gm. glucose.										Carb., gm.	Prot., gm.	Fat, gm.		Carb., gm.	Prot., gm.	Fat, gm.		
	Starv.	0.5.	1.	2.	3.	4.	5.												
7	200.0	202.0	303.0	285.5	224.7	211.6	204.0	103.0	5	5.0	159	59	102	0	164	64	107	66	13
8	169.0	222.0	242.0	282.0	312.0	274.0	222.0	173.0	5	9.1	115	56	102	0	125	57	103	48	3
19	222.0	284.0	306.0	306.0	316.0	322.0	250.0	100.0	5	18.0	112	62	127	40	125	62	127	41	3
20	161.3	236.8	286.5	392.0	312.5	263.0	266.6	230.7	5	16.6	126	61	123	20	115	56	100	33	3
21	277.7	303.0	350.9	401.0	392.0	377.0	392.0	127.0	5	5.5	106	60	120	45	120	64	150	50	3
22	160.0	168.0	281.0	431.0	370.0	333.0	285.0	277.8	5	26.0	172	71	130	6	172	71	130	35	1
23	168.7	200.0	290.0	392.5	444.5	337.3	290.0	277.8	5	5.4	140	69	138	20	160	70	156	62	1
24	200.0	319.0	495.0	473.0	361.0	273.0	211.0	265.0	5	20.0	115	56	102	34	122	58	101	65	2



keep the patient sugar free. The mild group were patients who had all shown normal starving blood sugars, seldom if ever spilled sugar, required no daily dose of insulin and tolerated more than 110 gm. of carbohydrate. The cases selected for this group on these clinical criteria were Cases 6, 7, 8, 9, 10, 13 and 25. The moderately severe group were patients whose starving blood sugars had not always been within the normal range, who spilled sugar after slight dietary indiscretions, who tolerated 100 to 115 gm. of carbohydrate and who required no insulin or only small doses. The cases selected for this group on these clinical criteria were Cases 11, 12, 14, 15, 16, 17 and 18. The severe group were those patients in whom the fasting blood sugar in the clinic had always been above the normal level and who required insulin daily to remain sugar free. The cases selected for this group were Cases 19, 20, 21, 32, 23 and 24.

The patients were instructed to eat nothing after their supper meal and to report to the clinic without eating breakfast. A fasting sample of blood was taken, the patient emptied his bladder and was then given 100 gm. of dextrose dissolved in 300 to 400 cc. of water. Blood samples were taken at periods of 0.5, 1, 2, 3, 4 and 5 hours. The urine was collected during the experimental period and examined for sugar by Benedict's method. The blood proteins were precipitated immediately and the sugar determined by the modified Folin-Wu method.<sup>11</sup>

**Results.** As a result of the tolerance curves the patients were again grouped into mild, moderately severe and severe groups. The criteria for these groupings were the fasting blood sugar level, the height of the hyperglycemia, its duration and the time required for the blood sugar to return to its starving level. On this basis we have considered as mild diabetics (Table 1) those patients whose starving blood sugar was normal but rose above the accepted value after the ingestion of 100 gm. of dextrose and yet showed a distinct fall at the third hour. The moderately severe group (Table 2) includes patients with a fasting blood sugar below 150 mg., a marked hyperglycemia following 100 gm. of dextrose and the persistence of this rise at the third hour of the curve. The severe group (Table 3) includes those patients in whom the starving blood sugar was above 160 mg. and in whom the hyperglycemia was maintained for the entire 5-hour period.

In the group of normals (Table 4) the results are similar to the normal curves reported by Gray<sup>1</sup> in his analysis of blood sugar standards. The blood sugars at the fourth and fifth hours showed a drop in 4 cases and a slight rise in 2. Several levulose tolerance curves had been done on Case 1, and the character of the curve corresponds to those of individuals who have been used to carbohydrate stimulation. The curve of Case 26, with renal glycosuria, is a normal curve, with the exception that the starving sugar level is lower than normal.

TABLE 4.—NORMAL.

Case No.	Blood sugar, mg. per 100.cc.							Greatest rise in mg. of bld. sug.	Period of hyperglycemia, hours.	Urine sugar, gm.
	Number of hours after taking 100 gm. glucose.									
	Starv.	0.5.	1.	2.	3.	4.	5.			
1*	100.0	91	86	77	73	57.0	64			
2 .	75.0	160	125	93	79	61.0	55	85	1	
3 .	76.0	121	133	133	44	57.0	66	57	2	0.65
4 .	84.0	156	113	80	71	82.0	92	72	1	
5 .	100.0	122	156	121	103	86.9	80	56	2	
26†	68.3	123	152	110	90	75.5	67	84	1	0.60

\* This patient had had several levulose tolerance curves done during the 10 days preceding this dextrose curve. The character of this curve corresponds to those of patients who have been used to stimulation of their carbohydrate mechanism.

† This patient is the renal diabetic.

**Discussion.** In correlating the clinical severity of the diabetes with the type of the glucose tolerance curve exhibited by each group, we found that in the mild clinical group 1 case (Case 25) had a curve of the moderately severe type. In spite of the character of the blood sugar curve in this patient, it is interesting to note that he continues to remain sugar free on an adequate diet with a carbohydrate content of 142 gm. In the moderate severe clinical group; 2 cases (Cases 17 and 18) showed curves characteristic of the severe type. In spite of the prolonged hyperglycemia these 2 patients do not require insulin and remain sugar free on diets containing 160 gm. and 142 gm. of carbohydrate respectively. In the severe group Case 17 is the least severe case, showing the lowest blood sugar at the fifth hour and one of the smallest rises in milligrams of blood sugar. The severe group as selected clinically all showed the prolonged severe type of tolerance curve.

The discrepancy between the clinical severity of the disease and the response to 100 gm. of dextrose followed for the 5-hour period requires explanation. It seemed to us that the patients who were exceptions to their clinical grouping probably have a higher renal threshold for sugar which is not exceeded by their ordinary divided carbohydrate intake. This is substantiated in Cases 17 and 18 by the fact that less sugar was spilled in the urine during the experimental period than in the other cases in the severe group. Another fact that must be considered is the rate of absorption. Case 17 is a cardiac patient with auricular fibrillation and, although the patient was fully digitalized and had no signs of congestion at the time the curve was done, the rate of absorption might have been lowered.

In analyzing the blood sugar curves in the mild group it seems to us significant that the 1 patient (Case 9) in whom the blood sugar

had not returned to the starving level by the fourth hour is the patient who continues to require a definitely restricted carbohydrate

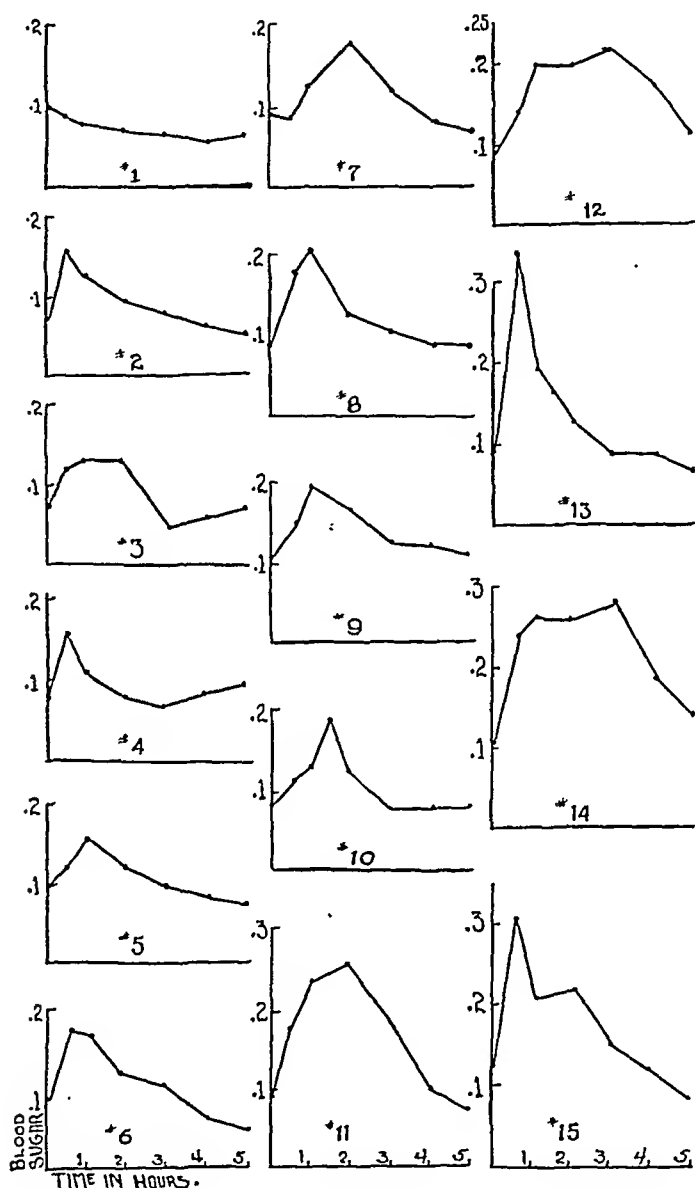


FIG. 1.—Chart of individual blood sugar curves of the cases reported.

diet. Three of the patients (Cases 6, 7 and 13) reached at the fifth hour a blood sugar level lower than their starving level. This may be explained on the hypothesis of MacLean and De Wesselow,<sup>6</sup>

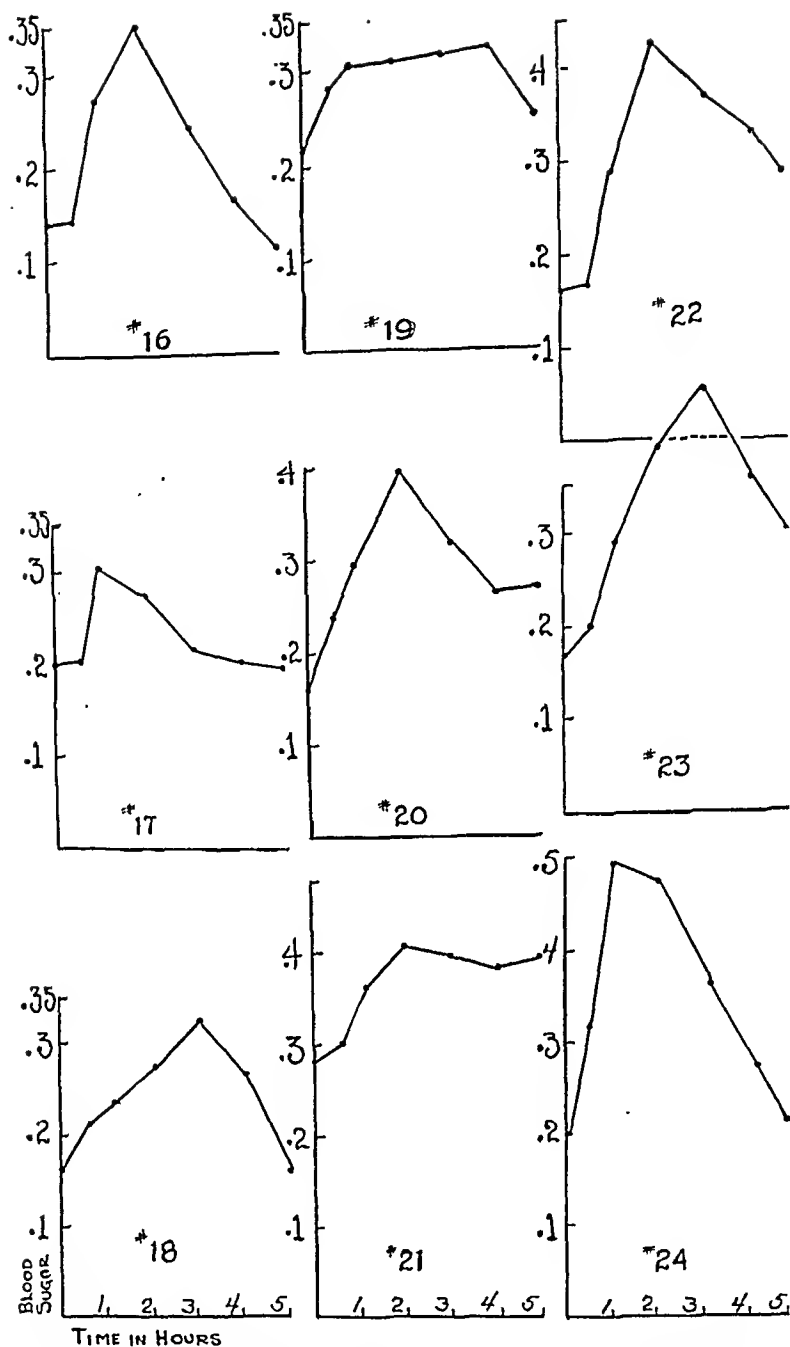


FIG. 2.—Chart of individual blood sugar curves of the cases reported.

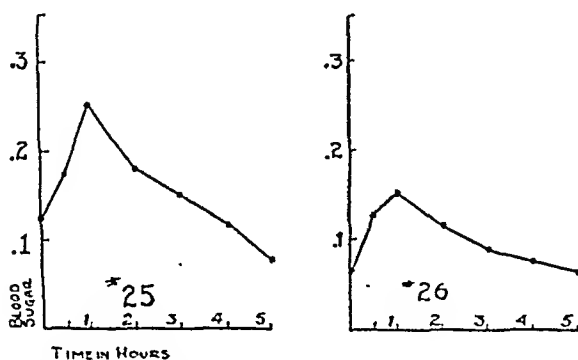


FIG. 3.—Chart of individual blood sugar curves of the cases reported.

supported by the observations of Foster,<sup>12</sup> that following the ingestion of glucose there is an overstimulation of the glycogen-forming function of the liver. Apparently in the mild diabetic this response is not abolished, whereas in the severe diabetic glycogen synthesis does not occur to any appreciable extent and hyperglycemia continues unchecked.

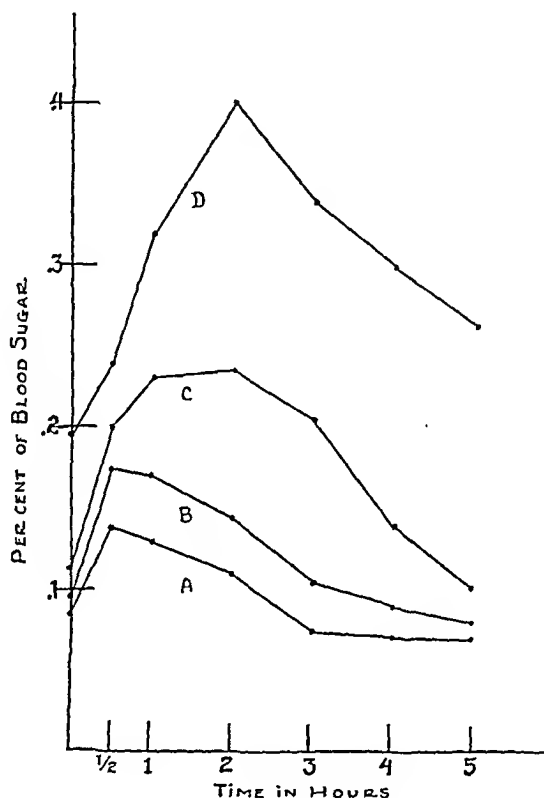


FIG. 4.—Average of the five-hour curves in the four groups studied: A, average of normal group; B, average of the mild diabetics; C, average of the moderately severe group; E, average of the severe group.

In the moderately severe group 3 cases (Cases 11, 15 and 25), with blood sugars at the third hour of 186 mg., 153 mg. and 150 mg., reached a normal blood sugar at the fifth hour. The other 3 cases all had blood sugars above 200 mg. at the third hour and at the fifth hour were still above 120 mg. Apparently the patient whose blood sugar is above 200 mg. at the third hour will not reach the fifth hour with a blood sugar below or equal to his starving level. This group also bears out the observation of Ohler,<sup>10</sup> that the fasting blood sugar gives only partial and often misleading information. In all but 1 of these patients the fasting sugar was below

148 mg. and, although the total rise in milligrams of blood sugar was greater in the patient with the higher fasting level, the hyperglycemia was not maintained for any longer period of time.

MaeLean and De Wesselow<sup>6</sup> studied the blood-sugar curve in a moderately severe diabetic over a five-hour period and found the initial blood-sugar level was not regained until the end of that time. This inability on the part of the diabetic patient to regain his starving blood sugar level seems to us to be of real clinical significance. The amount of carbohydrate at any one time should not so overload

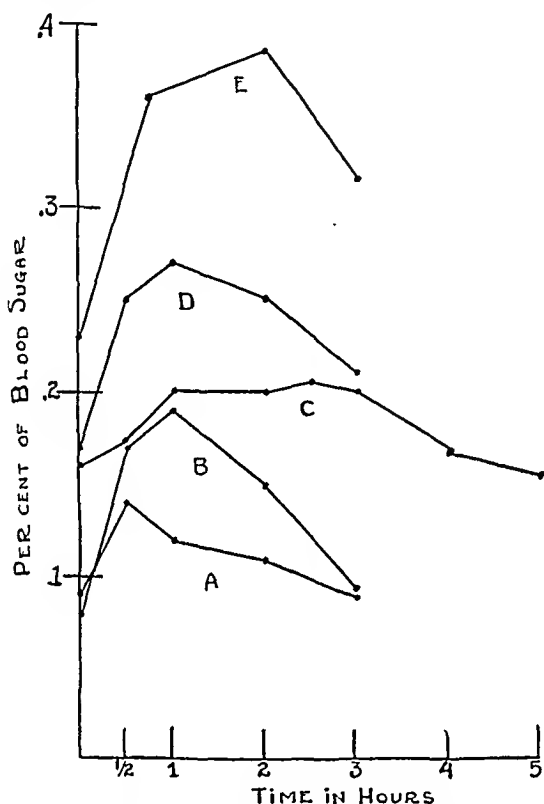


FIG. 5.—Three-hour blood sugar curves plotted from the results of other investigators. A, average of normals from Gray;<sup>1</sup> B, average of diabetics with fasting blood sugars below 120 mg. from Gray;<sup>1</sup> C, five-hour curve reported by MaeLean and De Wesselow;<sup>6</sup> D, average of diabetics with fasting blood sugars above 120 mg. from Gray;<sup>1</sup> E, average of Wishnofsky's 17 cases.<sup>4</sup>

the carbohydrate mechanism that the patient will reach his next feeding with an abnormal blood sugar level. The state of the blood sugar can readily be ascertained by doing a blood sugar before the next meal or 4 hours after the previous meal. This seems to us more important than a starving blood sugar.

In both the moderately severe and the severe group the blood sugar level at the third hour is distinctly abnormal. In the former group this level is lower than in the severe group. As mentioned previously, the lowest blood sugar curve in the severe group was

that of Case 17, who was classified as moderately severe clinically. The important fact in these two groups is whether or not the hyperglycemia is maintained. Can one assume that a blood sugar at the third hour below 275 mg., the highest in the moderately severe group, will fall to a reasonable level at the fifth hour? It seems to us that this question is best answered by an estimation of the blood sugar content at a later hour. The clinically moderately severe diabetic is the patient who manages to control his hyperglycemia by the fourth or fifth hour, regardless of its rise.

In the present study, with three exceptions, the classification, based on the clinical course of the diabetes, was confirmed by the glucose tolerance curves. In view of this, it would seem unnecessary to resort to a tolerance test for the purpose of estimating the severity of the disease, provided there is sufficient time to observe the patient under proper conditions. If this is not possible, and a tolerance test is used to establish the severity of the diabetes, we feel that the height of the blood sugar at the fifth hour gives more definite information on this point than the 3-hour test.

All the patients were seen in the clinic 3 to 5 days after the tolerance curves had been done. All were sugar free and had suffered no untoward effects as a result of the test. We have found no evidence of permanent or even transient impairment of the carbohydrate mechanism in any of the patients studied. Allen,<sup>13</sup> Ohler<sup>10</sup> and several other investigators warn of the disastrous effect of a large dose of glucose; we did not have this experience.

**Summary.** 1. The blood sugar curve following the ingestion of 100 gm. of dextrose was studied for a 5-hour period instead of the customary 3 hours in normal individuals and in mild, moderate and severe diabetics.

2. In the normal group the blood sugar reaches its height in from 0.5 to 1 hour. The blood sugar returned to a normal level at the second or third hour.

3. In the group of mild diabetics the return of the blood sugar to its starving level was at the third or fourth hour. The greatest hyperglycemia was at the first or second hour.

4. In the moderately severe group the return of the blood sugar to its starving level was delayed to the fourth or fifth hour. The greatest hyperglycemia occurred at variable periods.

5. In the severe group the blood sugar was markedly elevated for the entire 5-hour period.

6. There is evidence presented that a starving blood sugar level of over 160 mg. suggests that the patient will not return to this level within a period of 5 hours following the ingestion of 100 gm. of dextrose.

**Conclusions.** 1. It is suggested that the blood sugar level taken 4 hours after a meal is a better index of the severity of the diabetes than the starving blood sugar.

2. The severity of the diabetes as classified by clinical criteria was supported in all but 3 cases by the glucose tolerance test.

3. The 5-hour test is found to give more valuable information in many cases than the 3-hour test.

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### PSEUDONEOPLASTIC LUETIC GRANULOMATA.

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It is a commonplace of medical practice that syphilis in the protean manifestations of its tertiary stage may resemble almost any disease form. In bones and in other organs, where isolated luetic lesions have been more commonly reported, both the clinician and the roentgenologist have been on the alert especially for those



forms which simulate tumors. In or about muscles, however, syphilis appears to have a particular tendency to the formation of tumor-like growths. It is doubtless to the relatively rare occurrence of this form of the disease that the errors in diagnosis are to be attributed. Where these tumefactions are localized simulating benign growths the dilemma may not be as difficult or important to resolve as where they are infiltrating in nature. In these latter cases diagnostic misinterpretations may sometimes involve serious consequences as is shown by reference to the literature. In Chastenet de Gery's<sup>1</sup> case a recurring tumor and a mistaken biopsy specimen almost resulted in disarticulation at the hip; Deniker<sup>2</sup> reported a case in which the biceps cruris was resected; Köhler<sup>3</sup> described another in which he erroneously removed the muscles of one-half of the abdominal wall, while Planson<sup>4</sup> performed a myomectomy of the latissimus dorsi.

The occurrence of 2 such cases on our service within a relatively short time aroused our interest in the subject, and search of the hospital records unearthed 3 other somewhat similar cases occurring either in the muscle or fascia about the knee. They are presented in the hope that they may direct attention to this manifestation of lues and possibly save the patient an unwarranted operation and the surgeon unnecessary chagrin. Roughly, they may be divided into two main groups—one in which a discrete, apparently benign tumor formation was observed and a second in which a more diffuse invasion of the muscle led to the suspicion of a malignant neoplasm.

In the first group we present 2 cases:

**Case Reports.** CASE 1.—M. F., female, colored, aged 48 years, was seen in the Outpatient Department of the Hospital for Joint Diseases in 1921, complaining of a swelling of the left prepatellar region. The prepatellar bursa was excised and the patient made an uneventful recovery. In 1925 the patient returned to the dispensary, stating that a small tumor had developed slightly lateral to the site of the previous operation. This was painless, but was slowly growing in size. This mass was diagnosed as a benign tumor and was excised. The pathologic report was: "Gross: Specimen consists of a small nodule, measuring 1 cm. in its greatest diameter. This is a rubber-firm tissue; on section it is white. Microscopic (Fig. 1) sections show a fibrous nodule with numerous areas of perivascular round-cell infiltration; plasma cells and an occasional giant cell are to be seen. Diagnosis: gumma." The patient disappeared from the dispensary until March, 1928, when she again returned complaining of pain on walking. Careful examination disclosed a small hard nodule on the outer side of the knee joint with the knee in flexion. Roentgen ray of the knee showed a chronic productive osteoarthritis. When advised to take antiluetic treatment the patient demurred, and has not been seen since.

The next case is almost the exact parallel of the above case, though it appeared to arise beneath rather than in the muscle.

CASE 2.—J. P., male, colored, aged 30 years, was admitted to the hospital on November 10, 1930, complaining of pain and stiffness in the left knee.

The present illness began 6 months prior to admission, with slight pain in the left knee, occurring chiefly at night, and awaking him from sleep. The pain disappeared upon activity. About 3 months after onset he noticed a mass above and to the outside of the knee cap, which had gradually increased in size. The pain has increased in severity, and in the past month there has been some interference with motion of the knee upon arising in the morning. The patient was born in Porto Rico. He remembers no serious illnesses. His tonsils were removed 13 years ago. No history of venereal diseases could be elicited. The patient has been married 20 years and has a wife and 1 child living and well. There was no history of miscarriages.

*Physical examination* revealed a well-nourished, well-developed adult, with no significant physical findings, except for the local orthopedic condition. In the suprapatellar region, just beneath the vastus externus, there was a globular mass, about 4 cm. in diameter, of resilient consistency, not attached to the skin. The tumor mass was deeply situated and seemed to be attached by a fasciculus to the upper outer border of the patella, at which point there was some tenderness. The motions of the knee were normal. No fluid was present in the knee joint. Laboratory examinations revealed the following: Wassermann, 2+, with cholesterinized antigen. Blood count: White blood cells, 5400; polymorphonuclears, 34 per cent; lymphocytes, 55 per cent; eosinophils, 9 per cent; monocytes, 2 per cent; hemoglobin, 80 per cent. The roentgenologist reported "hypertrophic arthritis, with no pronounced bone atrophy." A tentative diagnosis of soft tissue tumor about the knee, fibroma or lipoma was made and operation advised.

At operation, on November 13, 1930, a 4-inch incision was made directly over the tumor mass in the lower external aspect of the thigh, exposing a tumor mass about the size of an egg, superficially covered with fatty tissue, of fibrous consistency and apparently situated beneath the muscles. The tumor extended distally to the patella, to which it was firmly attached and merged with the capsule of the joint. The mass was not incapsulated. The growth was dissected out *en masse*. At several points it was necessary to remove small portions of the suprapatellar pouch, exposing the joint cavity which showed an injected hypertrophied synovial membrane. The wounds in the joint capsule were repaired with chromic sutures, and the wound was closed in layers. Union occurred by primary intention. The tumor appeared completely benign and a postoperative diagnosis of fibroma was made. However, to everyone's great surprise, the pathologic report by Dr. Jaffee read as follows: "Gross: Specimen consists of a very firm piece of fibrous tissue, measuring 4 by 3 by 2 cm. Microscopic section (Fig. 2) reveals rather dense fibrous tissue, which shows evidence of a very extensive chronic granuloma. This is manifested by very dense lymphoid infiltration. In other places the formation of tuberculoma-like lesions, with numerous giant cells, is present. Some of the larger blood-vessels are surrounded by giant cells. These tubercle-like lesions show in places fusion into conglomerate masses. No caseation is present. Diagnosis: gunma." The patient was discharged with the wound fully healed, on November 23, 1930, and is now receiving antiluetic treatment in the Outpatient Department.

In the second group, in which the diagnosis of a malignant growth was made pre-operatively, we present 3 cases.

CASE 3.—W. G., male, white, aged 36 years, was seen at the clinic at the Hospital for Joint Diseases on November 24, 1930, complaining of a

large lump on the outer aspect of his right knee for the past 5 months. This mass was painless, very hard and had been gradually growing in size. There had never been symptoms of acute inflammation nor interference with motion of the knee. The patient walked without a limp. He observed that in the nature of his work at a machine, this mass had been continually exposed to slight blows against the machine. The patient was married. His wife and 2 children were living and well, but there was a history of several miscarriages in the family. The patient absolutely denied affliction either with lues or gonorrhea. A Wassermann performed on the outside was reported as completely negative.

Apart from the local condition, there were no positive physical findings. Over the anterolateral aspect of the right knee joint, extending from the lateral border of the patella to beyond the posterior border of the fibula, and from about the level of the tibial tubercle to the upper border of the outer condyle, there was a firm, somewhat lobulated, elastic, nontender mass, about 3 inches in its longest diameter, apparently fixed to the underlying structures and to a lesser degree, to the skin. There was no interference with the gait of the patient, no limitation of motion in the knee joint and no fluid, crepitus or abnormal mobility in the knee joint. The inguinal glands were not enlarged. The Roentgen ray was reported as showing no evidence of bone involvement, and a diagnosis of "pretibial soft tissue swelling" was made. The patient was admitted to the hospital on December 3, with a pre-operative diagnosis of tumor of the right knee joint capsule.

On December 4 a 4-inch incision over the tumor mass disclosed a grayish-red elastic, irregular tumor mass apparently attached to the lateral aspect of the knee joint, but not involving the joint itself. With some difficulty the mass was dissected away from the skin, the biceps tendon and the peroneal nerve which it surrounded. The upper portion of the tibialis anticus muscle was apparently involved in the growth and was dissected with the tumor mass. The wound was closed in layers.

Upon sectioning the tumor after its removal, we realized that we were dealing with a tumor mass that was not characteristically malignant, and which still did not belong to the group of typically benign tumors. A check-up Wassermann reported several days later first aroused our suspicion that we were dealing with one of the manifestations of syphilis. This suspicion was somewhat confirmed by the pathologic report of Dr. Jaffee, which is herewith appended: "Gross: Specimen consists of a flat piece of tissue measuring 8 by 5 by 1 cm. in thickness. Several sections taken showed a fibrous tissue. Joint capsule was also taken. Microscopic (Fig. 3): Sections show a thickened connective tissue, very densely infiltrated with lymphocytes, showing also large collections of lymphocytes about some of the bloodvessels, and in other areas showing epithelioid proliferations resembling but not typical of tuberculosis. Scattered through the sections there are some giant cells, one of the sections having a fairly large number. The same type of lesion is found in the capsule of the joint. The lesion is a granuloma. All tumors may be excluded. Tuberculosis, I believe, may also be excluded. The possibilities are that the lesion is syphilitic, though typical gummata are not observed. Diagnosis: Luetic (?) granuloma about the knee."

The record of the following case has been very graciously put at our disposal by Dr. Philip M. Graussman, surgical director at the hospital.

CASE 4.—M. K., male, aged 29 years, was seen in the Outpatient Department on October 21, 1928, complaining of a tumor in the lower portion of



FIG. 1.—Marked sclerosis, round-cell nodules and occasional giant cells. ( $\times 100$ .)

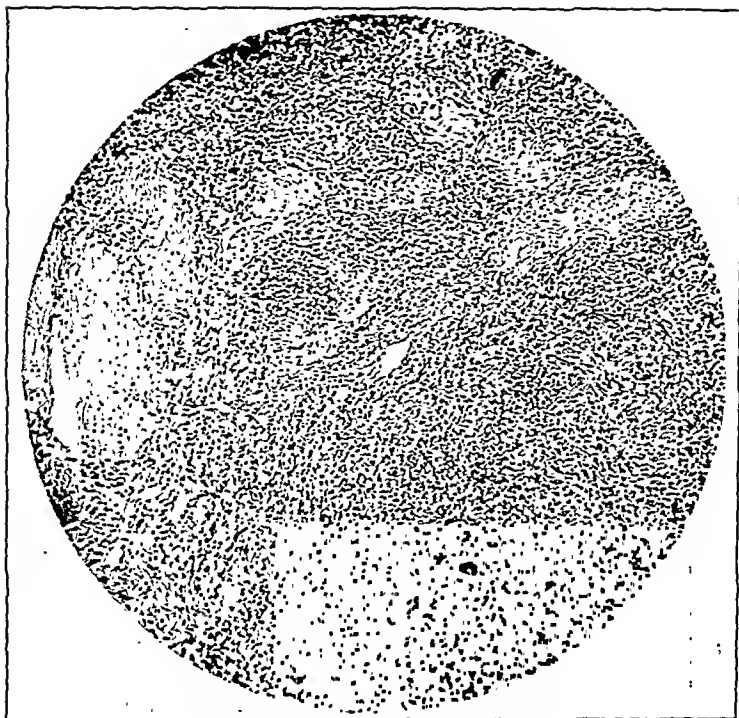


FIG. 2.—Dense lymphoid infiltration. ( $\times 110$ .)

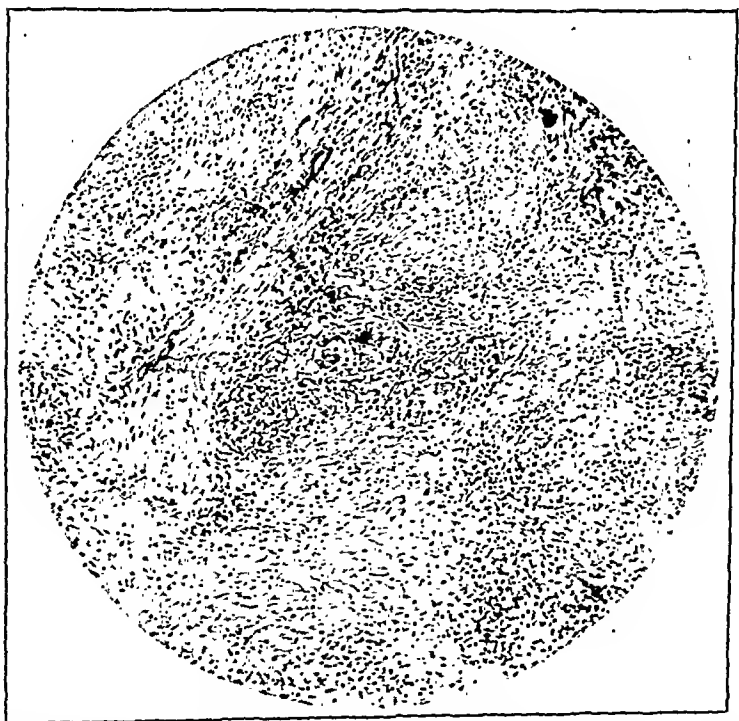


FIG. 3.—Sclerosis. Perivascular infiltration; epithelioid proliferation. ( $\times 110$ .)

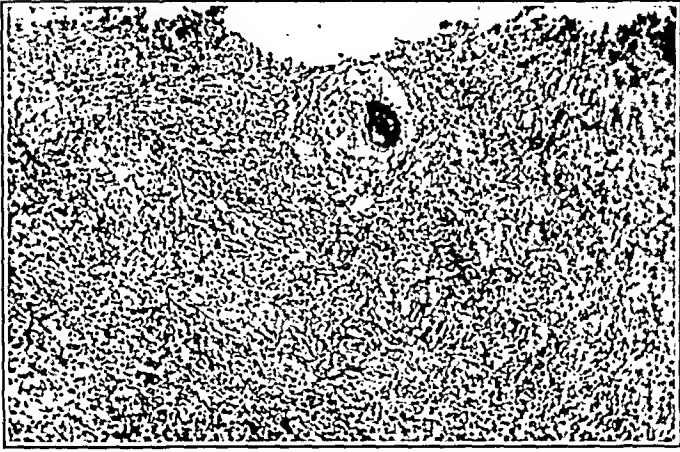


FIG. 4.—Edge of necrotic area. Epithelioid proliferation; occasional giant cell; lymphoid infiltration; sclerosis not as marked as in other specimens. ( $\times 120$ .)

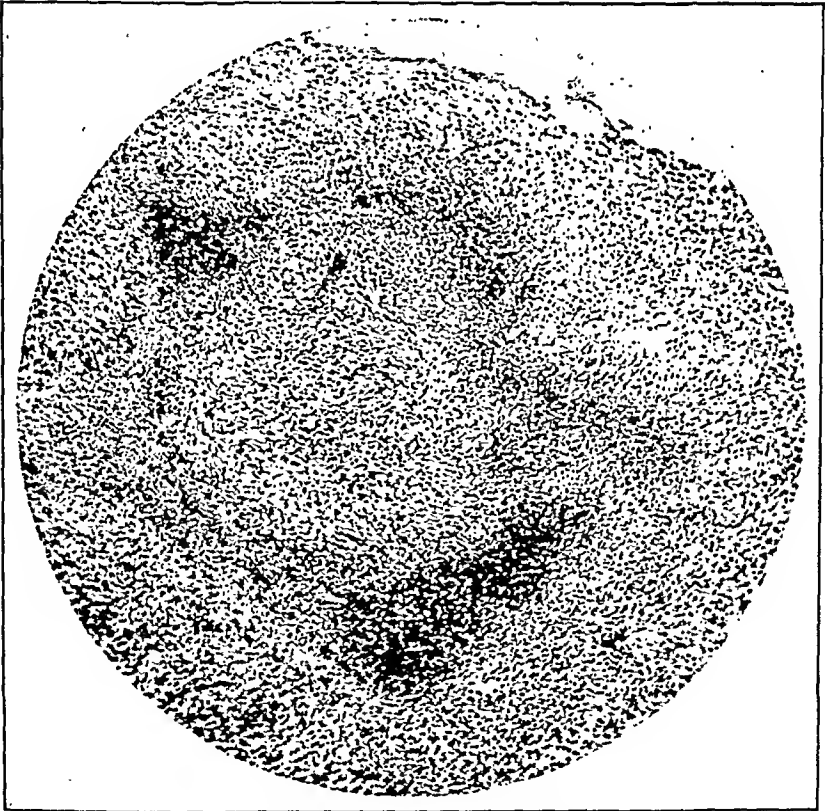


FIG. 5.—Gumma formation at edge of necrotic mass. ( $\times 100$ .)



the left thigh. This tumor was somewhat nodular in places and somewhat fluctuating in other places. The patient gave a history of chancre 14 years ago. He stated that he had received vigorous antiluetic treatment and had been told he was cured. All other manifestations of the disease were denied. Six months ago, without any other history of trauma, a mass which had been gradually growing in size was noticed on the inner aspect of the left thigh. The mass was not painful, appeared to be somewhat adherent to the skin on the inner aspect of the knee joint and its lower pole and was about the size of a large lemon. Beyond this nothing was found. In view of the history of lues, the patient was given rather intensive antiluetic treatment without any effects whatsoever. On November 1, 1928, the patient was admitted to the hospital with a diagnosis of neoplasm of the thigh. The Wassermann was 4+. The leukocyte count showed 12,000, with 80 per cent polymorphonuclears. On November 13, 1928, this patient was operated upon, and a tumor was found adherent to the muscles of the underlying structures. This was completely removed and the pathologist, Dr. Jaffee, reported: "Gross: Specimen consists of a tumor mass, measuring 8 by 5 by 4 cm., with several smaller pieces. This tumor mass has attached to it a piece of very firm aponeurosis. Part of it is encapsulated. On opening it, it showed a soft greenish-gray necrotic mass. Microscopic (Fig. 4): For the most part, the mass consists of complete necrotic tissue. It is surrounded by a very vascular granulation tissue with numerous lymphocytes and also areas in which there is an epithelioid proliferation and some giant cells. Diagnosis: gumma." The patient made an uneventful recovery and has since been lost sight of.

This last case is interesting because it was only after careful reëxamination of the slides in the light of the clinical history that the pathologist was enabled to ultimately arrive at a diagnosis.

CASE 5.—J. C., male, aged 36 years, colored, born in United States, was seen in the Outpatient Department of the Hospital in April, 1929, complaining of swelling of the left knee. He stated that on January, 1929, he had fallen and injured his left knee. The knee became swollen and slightly painful. The pain was somewhat intermittent in character, and some time later the patient noticed the development of a lump on the inner aspect of the left knee gradually growing in size. There never had been any interference with motion.

The patient denied chancre or other secondary luetic manifestations. In 1919 a lump was excised from the left groin. This lump was painful and attributed by the patient to an injury. In 1923 he was struck on the left knee by an automobile crank-handle; he made a slow recovery from this injury, but since then the knee has been painful in bad weather. In 1924 he was treated in the Harlem Hospital for gonorrhea and lues.

When first seen, in 1929, there was a freely movable swelling, the size of a large lemon, connected with the vastus internus muscle on the left knee. There was a moderate effusion into the knee joint, but no limitation of motion whatsoever in any direction. The tumor mass was painless, somewhat nodular in places and somewhat elastic in other places, and seemed to infiltrate the muscle. The pupils reacted to light and accommodation somewhat sluggishly. A slight systolic murmur was heard at the apex and was transmitted to the axilla only after exercise. All other physical findings were negative. In spite of the Wassermann test, which was reported 4+, it was clinically felt that this tumor mass presented too much the appearance of a malignant neoplasm to warrant delay. The patient was admitted to the hospital with a diagnosis of malignant tumor of the thigh.



On April 18, 1929, the tumor mass was exposed through an 8-inch incision made along the inner aspect of the thigh. The fascia over the mass was adherent to it and to the quadriceps tendon. The mass was found to consist of several smaller nodular masses occupying the whole thickness of the quadriceps muscle and tendon, and the vastus internus muscle. A large area of the quadriceps tendon and muscle and of the vastus internus muscle were excised to remove the tumor mass in one piece. In doing this, the joint was opened. The wound was closed in the usual manner, and the patient made an uneventful convalescence. The pathologist reported: "Gross: Specimen consists of a large piece of muscle and some fascia adherent to it. The muscles showed some areas of necrosis, some areas of marked interstitial myositis and other of yellowish caseation. Microscopic section (Fig. 5) showed numerous areas of necrosis and granulation tissue reaction. Evidences of an interstitial myositis. There are no evidences of gummata or syphilitic lesion. Diagnosis: abscesses of muscle with interstitial myositis." Following an uneventful convalescence, the patient was discharged from the Outpatient Department, where vigorous antiluetic treatment was resumed.

The history of lues with a positive Wassermann in the presence of an infiltrating tumor of muscle which on section showed the characteristic yellowish caseating areas of necrosis led us to believe that the myositis above reported was luetic in nature; we requested a revision of the slides. With the additional clinical information which we were able to supply, Dr. Jaffee restudied the slides, and after careful search found what he considered to be small gummata. The report was thereupon amended in the following sense: "Reëxamination of the slides shows at the periphery of the necrotic mass gumma-like formations. In view of the history and examination of the slides, believe the lesion is probably syphilitic."

Pathologically, tertiary muscular syphilis has been described as occurring in two main forms, and a third form which is a combination of the former two. The first type, the interstitial myositis, presents the picture usually found in other diffuse myositides and is characterized by vascular dilatation, infiltration of round and plasma cells, atrophy of the muscle fibers and increase of the interstitial connective tissue which leads subsequently to a diffuse sclerosis. This type, which is most frequently found in the sphincter ani, the masseter and biceps, is not of the tumor-forming variety, and does not enter into our consideration. It is the latter two, the gummatous and the sclerogummatous types, which present tumefaction and which may be said grossly to correspond to the two clinical types previously mentioned. The gummatous type, under which Cases 1 and 2 may be classed, is by far the commoner and occurs most frequently in the sternomastoid and in the crural muscles. It usually appears as a single lesion, but may be multiple and even symmetrical in its distribution. It is usually found in the belly of the muscle at the origin of the tendon and varies greatly in size. On section, it presents a whitish, reddish or yellowish appearance in which cascating areas may be seen. These necrotic centers increase in size until ultimately the whole mass may become completely necrotic. Microscopically, the muscle fibers are found separated and atrophied. In the connective tissue between the muscle bundles lie nodules of round and plasma cells, which may

or may not contain giant cells of the Langhan variety. As these nodules increase in size, their centers become necrotic and by their confluence present the picture of a tumor mass, necrotic in the center which is so characteristic of the larger gummata. In the combined or the sclerogummatous form of the disease both of these pathologic pictures are present in varying degrees. It appears, however, that the single caseating gumma is replaced by the appearance in the midst of a hard, infiltrating pseudoneoplastic mass of numerous miliary gummata of which Köhler says: "Such caseating foci situated in apparently sarcomatous masses can be considered as almost pathognomonic of syphilis." This is the type of lesion which was found in our Cases 3, 4 and 5.

Though Köhler considers the gross appearance so characteristic as to be pathognomonic, the differentiation from tuberculosis or other chronic infections may at times present the utmost difficulty. Indeed, even microscopically, the diagnosis may occasionally be impossible. Practically all of the pathologists who have discussed the subject agree that apart from the actual demonstration of the specific organism in the tissues, the differentiation between these miliary gummata and tubercles can at times not be made. In such cases the ultimate decision must rest with the clinician.

Because of the fact that the sclerogummatous forms may so closely resemble malignant neoplasms the clinical diagnosis is, of course, of vital moment in determining both the prognosis and the method of treatment. The history of exposure to luetic infection or the presence of a positive Wassermann reaction either in the blood or spinal fluid, associated with the appearance of a tumor in the muscles should always suggest the possibility of a sclerogummatous type of muscular syphilis. In such cases the reaction of the tumor mass to antiluetic treatment will be of determining moment. In fact, Nelaton remarked: "Every muscle tumor must first be treated with antiluetic measures." The disappearance of a large, apparently malignant muscular tumor under antiluetic treatment will determine its origin.

**Summary.** Five cases are presented in which operation was undertaken for tumors in or about muscles which subsequently proved to be luetic in nature. Attention is called to the fact that, both clinically and pathologically, the differential diagnosis between the relatively benign pseudoneoplastic luetic masses and true malignant tumors may be difficult. In all such cases operation should be deferred until careful tests, including the reaction to therapy, can be made to rule out the possibility of lues.

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## REVIEWS.

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FOOD ALLERGY. By ALBERT H. ROWE, M.S., M.D., Lecturer in Medicine in the University of California Medical School, San Francisco. Pp. 442. Philadelphia: Lea & Febiger, 1931. Price, \$5.00.

THE author has written comprehensively on the subject of food allergy. His most important contribution is the recommendation of elimination diets, which he devised. Their importance is appreciated when it is realized that 60 per cent of all patients with food sensitivity have negative skin reactions. Meticulous care is shown in the arrangement of these diets and in the directions for preparing them.

Not all clinicians and allergists can agree with Dr. Rowe in his statement that "Allergy, and as a part of it, food allergy, is probably next to infection the most common and important single etiologic agent in human symptomatology." Not all of us can accept as allergic or as possibly allergic all diseases of the gastrointestinal tract without demonstrable organic pathology; mucous colitis, proctitis, pruritus ani, gastrointestinal bleeding, tic douloureux, spasmodic croup, psoriasis, Ménières syndrome, dysmenorrhea, arthritis, arthralgia and epilepsy. Despite our skepticism, we envy anybody who can, by any method of treatment, obtain good or excellent results in 94 per cent of 400 patients with allergic disease.

S. L.

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INTESTINAL TUBERCULOSIS. ITS IMPORTANCE, DIAGNOSIS AND TREATMENT. By LAWRASON BROWN, M.D., Consultant to the Trudeau Sanitarium, and HORACE L. SAMPSON, Roentgenographer of the Trudeau Sanitarium, Saranac Lake, New York. Pp. 376; 122 engravings and 2 colored plates. Second Edition. Philadelphia: Lea & Febiger, 1930. Price, \$4.75.

A NEW edition, enlarged and revised, of a book which was the first authoritative presentation of the subject. This monograph gives an unusually thorough and complete discussion, with numerous case reports, many excellent illustrative roentgenograms and a full survey of the literature: it is truly the first and the last word on intestinal tuberculosis.

R. K.

HEALTH AT THE GATEWAY. By E. W. HOPE, O.B.E., M.D., D.Sc., Professor of Public Health, University of Liverpool; formerly Medical Officer of Health, City and Port of Liverpool. Pp. 213; illustrated. London: Cambridge University Press, 1931.

THE happily chosen title of this volume can scarcely fail to arouse one's curiosity as to its subject matter. Between its covers is packed a wealth of information concerning all of the major and most of the minor problems with which public health is concerned in the large seaport city of Liverpool. Unlike the general run of works dealing with public health, this one presents not only the experiences of the author during a long lifetime as health officer but also presents a scholarly review and interpretation of the various experiences of past generations upon which the modern development of public health measures has been based. It is impossible to pick out any single items for special comment, but mention should perhaps be made of the chapter dealing with the great plagues and pestilences of the past and of that concerned with maternal, infant and childhood morbidity and mortality. Despite the inclusion of much statistical material and of much reference to the political aspects of the problem, of public health, the author has succeeded in presenting the entire matter in the form of a most readable and altogether dramatic story which should appeal alike to the layman, the practitioner of medicine and to the public health officer.

C. E.

DIE CHIRURGIE DES KROPFES. By DR. KARL URBAN. Pp. 85; 51 illustrations. Leipzig and Wien.: Franz Deuticke, 1931. Price, M. 6.80; geb. M. 8.80.

A MONOGRAPH based on the personal observations of the author over a period of 30 years during which time he performed 4250 operations for goiter, with a mortality of only 0.9 per cent, the paper covers the entire range of the surgical treatment of disturbances of the thyroid in a clear and frank manner. The author is convinced that the best results are obtained from a subtotal resection of the gland ("enucleationresektion") taking care to leave behind a broad but thin capsule. He uses local anesthesia and nonabsorbable sutures. The former is preferred as he can keep better posted as to the condition of the recurrent laryngeal nerves and does away with the danger of asphyxiation in the large goiters. Chronic thyroiditis (Riedel-Struma) is discussed and a case reported in which the combination of Roentgen ray therapy and surgery was effectual. In discussing the prophylaxis of goiter he warns against the indiscriminate use of iodine and emphasizes the dangers of such administration. He finds no decrease in the incidence of goiter in Austria. Injuries of the parathyroids should not occur if his technique of

leaving behind a broad posterior capsule is followed. A pre-operative milk and vegetable diet also makes the occurrence of tetany less likely. The administration of parathyroid hormone is preferable to transplantation of parathyroids in cases of tetany. Injuries to the recurrent laryngeal nerve are more frequent than statistics indicate (10 per cent in the author's series), as a large proportion of them are only discovered by routine pre-operative and postoperative laryngoscopic examination. In the treatment of cachexia strumipriva he believes that transplantation of thyroid tissue is only of temporary value until the patient's thyroid remnants can resume their function. From a study of 3000 transplantations done in feeble-minded children he found that the transplant never lasted longer than 6 months and were usually resorbed sooner.

He discusses briefly the subject of benign metastasizing thyroid adenoma. The only one that he has observed was in a woman, aged 47 years, who developed tumors in her left femur and left clavicle 5 years after the removal of a cystic goiter. Surgery and Roentgen ray were effectual.

Three hundred cases of Basedow's disease have been treated by the author with a mortality of only 2.4 per cent. He states that the European form differs from that seen in America, being almost entirely the parenchymatous type, whereas ours are mainly the adenomatous type. While he does not feel that the European type can be safely treated with iodine, he refers to the brilliant results obtained in America from its use. He employs physical therapy, diet, fresh air and Roentgen ray treatment to a far greater degree than used in this country. As in the operation for simple goiter, he advocates a subtotal resection leaving a broad thin posterior capsule, preferring to remove too little tissue than too much and rather performing a secondary operation than leaving the patient with myxedema. He has only had to perform two such operations.

R. M., Jr.

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NERVOUS AND MENTAL DISEASE MONOGRAPH, SERIES No. 53.  
BRAIN AND PERSONALITY. By PAUL SCHILDER, M.D., PH.D.,  
Research Professor of Psychiatry, New York University. Pp. 136.  
New York and Washington: Nervous and Mental Disease Pub-  
lishing Company, 1931. Price, \$3.00.

THIS monograph, by a distinguished research worker of the psychoanalytic school, embraces two series of lectures: The Psychological Aspect of Cerebral Neuropathology and the Relation Between the Personality and Motility of Schizophrenies.

In the section on Encephalitis much important matter concerning the centers regulating sleep is correlated.

The "Id" is represented in the parts of the brain which are philo-

genetically older—around the cerebral ventriculi—and herein chiefly lies the disturbance in schizophrenics; the “Ego” is beyond this and is concerned with the confusional states; in the cortical layer are found the disturbances of agnosia, aphasia and dementia.

More formal treatment of the subject-matter would aid the reader not thoroughly conversant with psychoanalysis and, where possible a definite case report would be better than so much patchwork mixing of a case in the text.

There is a fair bibliography, but the index, said to be on page 137, is wholly absent. N. Y.

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THE THEORY OF OBSTETRICS. By M. C. DE GARIS, M.D. Pp. 272. New York: William Wood & Co., 1931. Price, \$5.00.

THE author has developed some new individual and interesting theories regarding certain obstetrical problems. His theory is a personal one and he supports it by a certain method of reasoning which may not appeal to all obstetricians. However, his intriguing speculation is stimulating and many of his subjects might well be considered. The author feels that uterine inertia is a central and fundamental problem of obstetrics and feels that underlying inertia uteri are albuminuric and pyelitic manifestations and, just as largely, hidden dental sepsis. He makes a plea for research and for a more careful individual analysis of obstetric results.

P. W.

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SURGERY: A HUNDRED YEARS AGO. Extracts from the Diary of Dr. C. B. TILANUS, afterward Professor of Surgery at the University of Amsterdam. Edited by PROFESSOR H. T. DEELMAN, professor of Pathology at the University of Gronigen, Holland. Translated from the Dutch by JOSEPH BLES. Pp. 156; illustrated. London: Geoffrey Bles, 1925. Price, 6s.

“THIS collection of letters, written during a tour made by three young Dutch doctors in the beginning of the XIXth Century, describes operations performed by great Continental surgeons such as Dupuytren and Larrey—before the use of anesthetics and aseptics. Most of these operations were marvels of surgical skill, and were considered none the less successful if the patient happened to die from *sepsis*, as was almost invariably the case.” The diary of one of them, Tilanus, has been abstracted and “introduced” by Deelman for our edification and a very entertaining account it makes. Then, as is now so often the case, the youthful students were especially interested in surgical operations, and the description of a long stay in Paris brings home all too clearly the fatal speeter of sepsis and the persistence of the will-of-the-wisp of phlebotomy as a panacea. Compound fractures vied with strangulated hernias and inflamma-

tion of the bowel as "captains of the men of death" and unfortunate indeed was the sick one who perforce fell into the hands of the surgeon. The relative merits of leeches, moxæ and cupping are discussed together with an interesting description of the hospital maternity arrangements of the day. Altogether this little volume offers a pleasant interlude in the past of our profession.

E. K.

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DER ELEKTRISCHE UNFALL. By DR. STEFAN JELLINEK, A.O. Professor der Elektropathologie an der Technischen Hochschule in Wien. Pp. 168; 50 illustrations. Third Edition. Leipzig and Wien: Franz Deuticke, 1931. Price, 8 M. (12s); 10 M. (15s.) bound.

Two more editions since this book first appeared in 1924, is a good record for such a specialized subject. Since then, also, it has become necessary to add chapters on accidents caused by the telephone, Roentgen ray, radium, explosions due to electricity and atmospheric conditions. In short space one can find a useful consideration of such topics as misconceptions and errors concerning electrical accidents, grounding and insulation, electrocution, apparent death, postmortem findings and methods of treatment. With the greatly increased contact of the public with electric contrivances of all sorts, such a work is most timely.

E. K.

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EARLY THEORIES OF SEXUAL GENERATION. By F. J. COLE, D.Sc. (OXON.), F.R.S., Professor of Zoölogy, University of Reading. Pp. 230; 21 illustrations. New York: Oxford University Press, 1930. Price, \$6.00.

As a relaxation from the preparation of a *History of Zoölogy*, the author has explored this "backwater" of his subject for the benefit of biologists. Beginning with Leeuwenhoek's discovery of the spermatozoa—"one of the major events in the history of zoölogy"—he carries us in eight chapters through the various developments of the Preformation Doctrine, Epigenesis (successive rather than simultaneous formation of parts), and Theories of Fertilization and Development.

Thus we may compare the prespermatozoal speculations by Paracelsus on generation from putrefaction with a translation of Leeuwenhoek's historic letter on spermatozoa (here first translated into English) and follow the hesitating acceptance of the significance of these bodies through succeeding centuries. The preformation doctrine is traced from Empedocles, Plato and Aristotle ("when a female mouse is dissected the female embryos appear to be pregnant") to its seventeenth century heyday. The

great Swammerdam, whose motto, "We must not surmise or invent, but discover, what Nature does, as Bacon very well says," is quoted on the title page of this book, uses the unpromising line of metamorphosis of insects to support his views that "the whole human race was comprehended in the loins of Adam and Eve," so that it must necessarily become extinct when the original supply of germ cells is exhausted. The account of the hard death of this doctrine at the hands of von Baer, literally centuries after Harvey's immortal "De Generatione Animalium," needs to be read in detail to be understood. Seldom has a mistaken scientific principle had so many eminent supporters in the face of potent opposition. The story is, indeed, an interesting one, and is here so well told that all biologists concerned with acquiring a perspective in their chosen field owe a debt of gratitude to the author. E. K.

## BOOKS RECEIVED.

### NEW BOOKS.

- Lehrbuch der Speziellen Pathologischen Anatomie, Vol. I.* By DR EDUARD KAUFMANN, Ord. Professor der Allgemeinen Pathologie und Pathologischen Anatomie an der Universität Göttingen, Geheimer Medizinalrat. Pp. 990; 506 illustrations. Leipzig: Walter de Gruyter & Co., 1931. Price, Rm. 55.—.
- The Note-Book of Edward Jenner.* With an Introduction on Jenner's work as a Naturalist. By F. DAWTREY DREWITT, M.D. (OXON.), F.R.C.P., formerly on the Committee of the British Ornithologists' Union and on the Council of the Zoological Society of London. Pp. 49; 1 illustration. New York: Oxford University Press, 1931. Price, \$1.25.
- An Introduction to Gynecology.* By C. JEFF MILLER, M.D., Professor of Gynecology, Tulane University School of Medicine. Pp. 327; 117 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, \$5.00.
- Egypt: The Home of the Occult Sciences: With Special Reference to Imhotep, the Mysterious Wise Man and Egyptian God of Medicine.* By T. GERALD GARRY, M.D., M.Ch., M.A.O., M.B.E., Senior Physician, Anglo-American Hospital, Cairo; Physician, Royal Terme, Montecatini. Pp. 93. London: John Bale Sons & Danielsson, Ltd., 1931. Price, 7/6d.
- Collected Papers of The Mayo Clinic and The Mayo Foundation, Vol. 22, 1930. Published May, 1931.* Edited by MRS. MAUD H. MELLISH-WILSON, RICHARD M. HEWITT, B.A., M.A., M.D., and MILDRED A. FELKER, B.S. Pp. 1125; 234 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, \$13.00.
- A Clinical Study of Addison's Disease.* By LEONARD G. ROWNTREE, M.D., and ALBERT M. SNELL, M.D., Division of Medicine, The Mayo Clinic and The Mayo Foundation. Pp. 317; 41 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, \$4.00.
- Proctoscopic Examination and the Treatment of Hemorrhoids and Anal Pruritus.* By LOUIS A. BUTE, B.A., M.D., F.A.C.S., Section on Proctology, The Mayo Clinic, and Associate Professor of Surgery, The Mayo Foundation. Pp. 178; 72 illustrations. Philadelphia: W. B. Saunders Company, 1931. Price, \$3.50.



*The Surgical Clinics of North America, Volume 11, No. 3 (New York Number, June, 1931).* Pp. 239; 73 illustrations. Philadelphia: W. B. Saunders Company, 1931.

*The Medical Clinics of North America, Volume 14, No. 6, and Index Volume (New York Number, May, 1931).* Pp. 300; 305 illustrations. Philadelphia: W. B. Saunders Company, 1931.

*International Register of Spas and Medicinal Waters.* Pp. 20. London: Headley Brothers, 1931. Price, 1s.

*Clinical Dietetics.* By HARRY GAUSS, M.S., M.D., F.A.C.P., Instructor in Medicine, University of Colorado, School of Medicine; assisted by E. V. GAUSS, B.A., formerly Assistant Dietitian, Presbyterian Hospital, Denver. Pp. 490; 59 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, \$8.00.

*Fighting Disease with Drugs.* A Publication of The National Conference of Pharmaceutical Research. Edited by JOHN C. KRANTZ, JR., with an Introduction by DR. JAMES H. BEAL. Pp. 230; illustrated. Baltimore: The Williams & Wilkins Company, 1931. Price, \$2.00.

*Accidental Injuries.* By HENRY H. KESSLER, A.B., M.D., F.A.C.S., F.A.P.H.A., Medical Director, New Jersey Rehabilitation Clinic. Pp. 718; 157 illustrations. Philadelphia: Lea & Febiger, 1931. Price, \$10.00.

*International Studies: The Prevention of Disease.* Conducted for The Milbank Memorial Fund, Vol. 2, Belgium, France, Italy, Jugo-Slavia, Hungary, Poland, Czecho-Slovakia. By SIR ARTHUR NEWSHOLME, K.C.B., M.D., F.R.C.P. Pp. 249. Baltimore: The Williams & Wilkins Company, 1931.

*Clinical Observations on the Surgical Pathology of Bone.* By DAVID M. GREIG, M.B., C.M., F.R.C.S. (EDIN.), F.R.S.E., Conservator of the Museum of the Royal College of Surgeons of Edinburgh. Pp. 248; 224 illustrations. Edinburgh: Oliver & Boyd, 1931. Price, 30/-net.

*Pediatric Education.* Section on Medical Service. Committee on Medical Care for Children. Report of the Subcommittee on Medical Education. BORDEN S. VEEDER, Chairman. Presented at Meeting of Section on Medical Service, Washington, D. C., February 20, 1931. Pp. 109. New York: The Century Company, 1931.

The findings of the Subcommittee on Medical Education is presented in this pamphlet together with their recommendations as regards both undergraduate and postgraduate instruction in this phase of medical science which has heretofore been grossly neglected for a subject so valuable to the welfare of the Nation. No school can give an adequate course in diseases of children and its allied branches without sufficient and properly equipped hospitals and clinics, manned by efficient and experienced professors and assistants. The curricula are outlined together with the recommendation of the number of hours to be devoted to this branch. It is further recommended that the teaching of pediatrics should be carefully studied for the purpose of making improved recommendations at a subsequent time.

A. S.

## NEW EDITIONS.

*Hypertension and Nephritis.* By ARTHUR M. FISHBERG, M.D., Associate Physician to Beth Israel Hospital and Adjunct Physician to Mount Sinai Hospital, New York City. Pp. 619; 38 illustrations. Second edition, thoroughly revised and enlarged. Philadelphia: Lea & Febiger, 1931. Price, \$6.50.

*Recent Advances in Pulmonary Tuberculosis.* By L. S. T. BURRELL, M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), Senior Physician to Royal Free Hospital. Pp. 240; 49 illustrations. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1931. Price, \$3.50.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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AND

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**The Pathologic Physiology of Pellagra.**—A series of five papers on this extremely important disease has recently been published by TURNER (*J. Clin. Invest.*, 1931, 10, 61). These papers represent a very thorough study of the disturbed physiology of a disease which is perhaps as important a disease from the point of view of the morbidity-mortality rate and economic loss as any disease which occurs south of the Mason and Dixon Line. A very large number of these cases are recognized each year in the far south and a very considerable number of them, at least in the early stages, go unrecognized. In this study of Turner's the first paper deals with detailed clinical data of 42 patients—sex, age, presence or absence of skin lesions and the severity, occurrence of diarrhea, sore tongue, psychoses and neuritis are considered in a most comprehensive table. Other clinical data are also included. The laboratory studies are based on estimations of the blood volume, plasma volume, red blood cell volume, as well as that of the packed red blood cells. Serum albumin, globulin, as well as the blood calcium, inorganic phosphorus, chlorids, CO<sub>2</sub> capacity of the plasma and total fixed base, are included. The second paper deals more in detail with the studies made on the serum albumin and globulin. In this group of patients it was found that there is a marked tendency for an extremely low serum albumin concentration which persists for a considerable period of time after the usual evidences of the disease have gone and despite a diet which is considered adequate. Turner attributes this to disturbed digestion with a low absorption of proteins as a result of injury of the digestive system by the disease. The serum protein determinations aided considerably in estimating the severity of the disease and in furnishing a criterion of cure. Paper No. III details the studies which were made upon serum calcium and phosphorus. Of particular interest in this communication is the hypothesis advanced that serum calcium concentration abnormalities in pellagrins are related in some way to disturbances of the nervous system. This may be causal or incidental. The next paper has to do with the serum electrolytes and acid-base equilibrium. The diminution in serum electrolyte concentra-

tion apparently is of considerably more importance than disturbance of acid base equilibrium in the pathologic physiology of this disease. The diarrhea and at times the vomiting that occur in this disorder seem to be the factor chiefly responsible for the low electrolyte concentration of the blood serum of the pellagrins. The last paper in the group is a study of the circulating blood volume in 41 pellagrins. In this group of patients the findings were as follows: 68 per cent of the group showed plasma volumes below normal and 32 above normal. The median was  $-4$  per cent deviation. The red cell volumes in 95 per cent of cases were below normal, with a median of  $-35$  per cent deviation. The total blood volumes in 82 per cent of these pellagrins were below normal, with a median of  $-17$  per cent deviation from ideal. Probably the most interesting clinical observation from these studies on the blood volume lies in the suggestion that certain skin abnormalities in chronic pellagra may be the result of deprivation of the skin of an adequate blood supply for a considerable time, although there is a concomitant (presumably) engorgement of the abdominal viscera. It is impossible to go into the details of these studies, but any one who is interested in a most remarkable disease whose manifestations differ in many ways from the usual run of disease, will find these studies stimulating as well as instructive.

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## SURGERY

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UNDER THE CHARGE OF

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**Derangements of Semilunar Cartilages.**—MACCAUSLAND (*Ann. Surg.*, 1931, 93, 649) states that the removal of a semilunar cartilage according to his technique (described in full in his paper) is followed in the majority of cases by a result entirely satisfactory to the patient. The best results are obtained in cases of young adults when the offending cartilage is removed within a short time of the trauma. A guarded prognosis must be given in cases with any arthritic tendency, which includes cases of long standing that show definite hypertrophic changes at operation and cases of older patients, that is those beyond middle life. Particular attention should be given to the treatment of mild injuries. If a slightly damaged cartilage is neglected it exposes the joint to progressive arthritic lesions. The most reliable diagnostic features are a definite history of trauma; recurrent periods of disability with local pain, slipping, effusion and swelling, initiated usually by some minor injury or twist; acute local tenderness at the point of attachment of the cartilage where the damage is located with a tendency for the tenderness to persist at this point; locking, that is, sudden inability to extend the joint fully; the absence of the cartilage thrust; the presence of an early pathologic lesion, such as tuberculosis or syphilis, must be borne in mind when operation for the removal of the cartilage is advised.

**The Use of Exploring Needles and Shadow Casting Media in the Diagnosis of Hepatic and Perihepatic Abscess.**—WILMOTH (*Ann. Surg.*, 1931, 93, 722) says that the exploring needle has a definite place in the diagnosis of hepatic and perihepatic abscess, and when used for injection of iodized oil the definite location, size and shape of the abscess can be determined. The site of the abscess is not entirely sufficient datum for successful treatment, but the extent of the cavity in all directions is important. The aspirating needle cannot be used with safety in the left lobe of the liver, in left perihepatic spaces. The exploring needle can be used without a general anesthetic. In the acutely ill patient the procedure gives no appreciable shock and the subsequent incision and drainage, if indicated, can be by the route that is shortest and least shocking. The spinal puncture needle or similar blunt needle adds to the safety of the procedure. The aspirating needle is of value both in diagnosis and in treatment of amebic abscess of the liver, or of those that have extended into the perihepatic spaces, provided secondary infection has not occurred. The presence of pyogenic organisms is an indication for incision and drainage. There is usually only one satisfactory route of approach to a hepatic or perihepatic abscess, and that route can be determined in the majority of cases by the definite localization of the boundaries of the cavity after injection of some opaque substance.

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**Twenty-five Years' Study and Survey of Syphilis.**—McDONAGH (*Urol. and Cutan. Rev.*, 1931, 35, 123) writes the period opens with the advent of the syphilitic trias and closes with the unitary view of the disease. The trias includes the discovery of the *Spirochaeta pallida*, the Wassermann reaction and arsenobenzene. When it was seen how quickly the signs and symptoms of syphilis vanished under arsenobenzene it was no longer thought necessary to keep the patient under treatment for two or more years. The treatment became symptomatic and its efficacy appeared to be confirmed by the number of fresh infections which occurred. The next stage was the increase of neurorecurrences. In fact, the incidence rose as the treatment became more spasmodic and gauged by the Wassermann reaction. Later, when it was found necessary to make the treatment more intensive and continuous, no fresh infections occurred, proving that what were considered at first to be fresh chancres were really recurrent chancres. Treatment alone does not diminish the incidence of an infection. Waves suggestive of an increase of syphilis appear from time to time, and the advent of another wave would render it again one of the biggest scourges. Syphilis sleeps—it is not dead or dying. What is most to be deplored is the gradual disappearance of clinical diagnosis, which brings even worse in its wake, the inability of the physician to learn his patient. Clinical acumen is the highest attainment to which a physician can aspire and learning and knowing the patient are going more than half way to ridding him of disease. Despite all the so-called "epoch-making" discoveries of recent years, the present state of medical science is not one to be proud of and the outlook to the author is far from hopeful.

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**Infective Granuloma.**—MACK (*Surg., Gynec. and Obst.*, 1931, 52, 672) reports that infective granulomata are far more frequent than the

literature on this subject would lead one to believe. The condition is directly due to a low-grade infection, causing an impairment to the circulation, or to an impairment of the circulation followed by a low-grade infection. In either case there is an inflammatory reaction characterized by a necrosis and a reparative process acting and reacting with a gradually increasing building up of an inflammatory mass, until a granuloma reaching even the size of a coconut has formed. Occasionally the reparative process predominates early in the condition, and one finds a constricting or stenosing granuloma. Infections within the gastrointestinal tract, such as appendicitis or diverticulitis, ulcers either within the stomach or in the intestine, foreign bodies within the bowel lumen, in the wall of the bowel or lying in the abdomen, such as purse-string sutures, lap pads or instruments left in the abdomen, splinters penetrating into the abdomen, may become the nucleus for the foundation of an infective granuloma. Trauma is a frequent cause for the condition, especially trauma, which results in a tear of the mesentery which allows foreign material to remain in the abdominal cavity or which may cause an undiagnosed and nonfatal perforation or laceration of the intestinal wall. Extraperitoneal inflammations may spread to or involve the gastrointestinal tract in the granulomatous mass. The diagnosis of carcinoma is most frequently made when an infective granuloma exists. Many of our recovered cases of inoperable carcinoma of the gastrointestinal tract have undoubtedly been granulomata. A more careful study of all cases of infective granuloma will enable an increasing number of correct pre-operative diagnoses to be made. The etiology, the similarity in the chain of symptoms, the characteristic findings at operation and the ability to make the diagnosis on histologic study warrant considering infective granuloma as a definite disease entity. In the presence of a tumor mass within the abdomen the possibility of an infective granuloma should always be taken into consideration in making the diagnosis.

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## THERAPEUTICS

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UNDER THE CHARGE OF

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AND

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**The Treatment of Angina Pectoris With Glucose.**—HASSENCAMP (*Zeitschr. f. Kreislaufforsch.*, 1931, 23, 132) discusses the probable mechanisms involved in Büdingen's intravenous injections of glucose solutions in the treatment of angina pectoris. He points out that Büdingen's original conception of the cardiac condition resulting from

hypoglycemia was entirely erroneous, due to errors on the part of the laboratory in the determination of blood sugar. Nevertheless the use of glucose has proved a valuable therapeutic procedure in many cases of angina. First, by supplying an excess of readily available sugar to the heart muscle; second, probably by alterations in the physical properties of the cells there are colloidoclastic and osmotic effects, and finally, through the relaxation of spasm in the smaller coronary branches. In treatment he employs freshly made solutions of pure glucose in freshly distilled water, beginning with an injection of approximately 30 cc. of a 10 per cent solution and increasing to 50, 80, 100, 150 and even at times to 200 cc. of a 10 to 20 per cent solution. He emphasizes that no fixed schedule of doses can be established, but that each patient must be treated according to his individual responses and that many patients have definite upper limits to the dose tolerated, above which the injections produce constitutional symptoms. Customarily he administers three injections weekly, though at times only two can be given. Better results are obtained from the use of the larger volumes of more dilute solution than from smaller volumes of more concentrated solutions. In those patients whose angina pectoris is complicated by other cardiac symptoms, namely, congestive failure and renal disturbances, the doses should range from 10 to 50 cc. of a 15 to 20 per cent solution, and it is frequently of great value to add from 0.2 to 0.3 mg. of strophanthin to the solution or, where a diuretic is needed,  $\frac{1}{2}$  cc. (50 mg.) of theobromin ethylenediamin. Even in cases complicated by diabetes it is possible to employ the sugar treatment with excellent results and without detriment to the diabetes. In general the sugar treatment must be continued from four to six weeks to obtain fully satisfactory results but, when secured, these frequently last for many months, even up to several years. The most satisfactory results are obtained in patients suffering from the angina of effort, while those with the angina of rest and angina complicated by cardiac weakness or renal insufficiency give less uniformly satisfactory results and results which, in general, are less permanent.

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**Medical Opinions on Circulatory Hormone Preparations.**—In an effort to secure some trustworthy conclusions concerning the value of several of the so-called hormone preparations derived from the heart, voluntary muscle and certain glandular organs such as the liver and pancreas, R. VON DEN VELDEN (*Deutsche med. Wchnschr.*, 1931, 57; April 10, page 619; April 17, page 672; April 24, page 712 and May 1, page 753), records and analyzes the replies to a questionnaire from more than 40 leading internists in Europe. It is evident, from the answers secured, that opinion as to their therapeutic value is highly contradictory. Despite the fact that certain investigators have apparently been able to demonstrate biologic activity of these preparations when tested upon animals and surviving animal organs, the majority of clinicians feel that these preparations exert no influence upon the cardiac rate or rhythm or upon the electrocardiogram and the majority finds that they are without influence upon the action of digitalis upon the heart of man. Some investigators report more or less satisfactory results from their use in angina pectoris, while the majority find them either to be without effect in this condition or distinctly inferior to the

usual drugs employed such as the nitrites and the xanthin derivatives. The same conflict of opinion concerning their observed effects upon elevated blood pressure is expressed by the various internists, although here many are inclined to believe that they are of definite value in lowering the blood pressure in the condition of essential hypertension, particularly where the pressure normally shows wide spontaneous variations. Both in the case of angina and of essential hypertension however, many of those who record some favorable results express the opinion that these are limited to those patients who are definitely of the neurotic type and that the results can be explained on the basis of psychotherapy, similar results being frequently obtained in the same patients from other forms of treatment. The author states it as his opinion that there is some promise in this form of therapy but scarcely dares to go further in its recommendation. He believes that its clinical use constitutes the treatment of ill patients with very uncertain remedies. In addition to this great uncertainty in the action of these substances, attention must be called to the fact that many clinicians have observed distinctly unfavorable side actions following their administration, especially following their intravenous or intramuscular injection.

NOTE.—A critical analysis of the replies indicates that these agents should not be accepted for clinical use in the present state of their development. It seems certain from the evidences presented that they are extremely untrustworthy, if indeed they have any definite actions upon the circulation other than those common to nonspecific protein split-products.—EDITOR.

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## PEDIATRICS

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UNDER THE CHARGE OF

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OF PHILADELPHIA.

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**Impetigo Contagiosa Neonatorum.**—SWENDSON and LEE (*J. Am. Med. Assn.*, 1931, 96, 2081) state that impetigo contagiosa neonatorum in nurseries for the newborn has become a serious problem of the modern hospital. It is practically impossible to prevent the occurrence of sporadic cases in nurseries. Constant vigilance for the detection of pyogenic infections in attendants and nurses and patients, and a nursery technique discouraging the development of pyodermic infections in newborn infants, is necessary in order to prevent epidemics of the disease. Epidemics are best controlled by means of a three nursery system which allows of segregation of infected babies, exposed babies and babies that have not been exposed from one another. They recommend a dry treatment of the lesions with the avoidance of the use of ointments. In this technique a bath is given every other day. Very little soap should be used and the skin should be dried by patting rather than by rubbing. After the bath the entire body should be

heavily coated with a dusting powder containing mercurous chlorid, 3 parts; taleum, 2 parts, and zinc oxid, 1 part. On the alternate days the babies should be examined for skin lesions, the buttocks should be cleansed with sterile oil and the dusting power again applied. The powder stains the clothing gray. If irritation develops taleum should be temporarily substituted. Excessive warmth and moisture of the skin should be avoided by dressing the babies lightly.

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**Inhalation Method of Resuscitation from Asphyxia of the Newborn.**—**HENDERSON** (*Am. J. Obst. and Gynec.*, 1931, 21, 542) recommends the simplest apparatus, consisting of a small cylinder of a mixture of oxygen and 7 per cent carbon dioxid, with a mask to enclose the face and a rubber bag of only 2- or 3-liter capacity, with a valve or stopcock at the end. The bag is filled and the cylinder cut off. The mask is held on the face while the bag is squeezed to make a gentle pressure sufficient to cause a succession of slight dilatations of the baby's lungs. Then, as spontaneous breathing begins, the inhalation is continued, or, if desired, mouth-to-mouth dilatation may be used and then the inhalation administered. It is the inhalation and its stimulating effects on natural breathing rather than any form of artificial respiration that is most important. This inhalation should be given several times a day for five or ten minutes for several days. He recommends its use not only for asphyxiated babies but also for normal babies. The object of this latter recommendation is to insure full dilatation of the lungs. When this inhalation is universally adopted instead of the old method of making the child cry, the large number of babies that die of pneumonia consequent to a persisting atelectasis will be saved as well as those that can be resuscitated most effectively by this method from primary birth asphyxia. The essential point regarding birth asphyxia is that, as a result of diminished blood supply to the brain during prolonged labor, the sensitiveness of the respiratory center is depressed. In the normal child the respiratory center is stimulated, as soon as the placental circulation slows down, by the carbon dioxid formed in the child's own body. In the asphyxiated child, although there may be more carbon dioxid than normally, the center is so depressed that this stimulus is insufficient to excite natural breathing. When a sufficient quantity of carbon dioxid is supplied to the lungs the center responds normally.

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**Prognosis of Acute Glomerular Nephritis in Children.**—**GUILD** (*Bull. Johns Hopkins Hosp.*, 1931, 48, 193) studied 34 patients from 1 to 12 years after an acute attack of glomerular nephritis. He found that in this condition in children the prognosis is good and, in general, the younger the child the better the prospects of complete recovery. Albuminuria may persist for years without impairment of general health or kidney function. It may also disappear completely after it has been present at least as long as a year. Children who have once had acute nephritis stand subsequent infections without greater liability to complicating renal disease than is shown by children who have never had nephritis. Although many of the patients are now entirely normal in spite of neglect of foci of infection following the attack of



nephritis, the fact that several of those now showing some abnormality are among those neglected suggests that it is wise to attend to such foci promptly in all cases. It is of the utmost importance to follow those patients with albuminuria to determine the ultimate results.

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**Treatment of Acute Cerebral Complications of Nephritis.**—ALDRICH (*Am. J. Dis. Child.*, 1931, 41, 1265) studied the clinical records of 28 patients who showed cerebral symptoms in the course of hemorrhagic types of nephritis. He attempts to explain the behavior of these patients on this hypothesis. Owing to an intoxication that is probably the cause of the nephritis, the tissues, including those of the brain, take on water and become edematous. This water is considered to be held in chemical combination with the tissue cells. The resulting edema of the brain causes increased intracranial pressure, a compensatory rise in the blood pressure and clinical symptoms. The general increased affinity of the tissue cells for water results in oliguria and usually in subcutaneous edema. When large amounts of fluid are given there is a tendency to dilute the toxins and to provide free water for their elimination through the kidneys. Thus paradoxically, the administration of water may reduce edema. In this process, when the cerebral edema is decreased, the intracranial pressure and the systemic blood pressure fall, giving relief from the cerebral symptoms. Following this, as more water becomes available for excretion, diuresis takes place. When the onset of coma makes the adequate administration of fluid impossible, intravenous injections of strongly dehydrating salts, such as magnesium sulphate, shrink the cerebral tissues, leading to prompt relief from the symptoms and allowing the administration of fluids by mouth. The administration of magnesium sulphate by mouth in large doses seemed to hasten recovery, and did not cause loose stools in edematous patients until the symptoms had disappeared. It is believed that when given orally this salt acts in the same manner as when given intravenously.

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**Comparative Studies on Calcium Gluconate and Other Calcium Salts.**—LIEBERMAN (*J. Am. Med. Assn.*, 1931, 97, 15) studied the effect of calcium gluconate on human beings and dogs when given orally, subcutaneously and intravenously. This compound can be given in repeated and adequate amounts subcutaneously without causing either irritation or necrosis. Three or 4 gm. a day after meals seemed to be the proper dose for an adult. Blood calcium attains its maximum elevation within an hour after subcutaneous or intramuscular administration of calcium and within four hours after being given orally. Urinary calcium appears to be a qualitative index of the state of the blood calcium level. Whether this is true in all pathologic states remains to be seen. A urinary value of about 10 to 20 mg. per hour appears to be most desirable in avoiding either a hypercalcemia or a hypocalcemia. Intravenous calcium therapy is dangerous because of the danger of sudden intravascular clotting and death. Highly suggestive digitalis-like effects of calcium were observed, but could not be explained.

## DERMATOLOGY AND SYPHILIS

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**Apparent Specific Effects of Sodium Iodide in Herpes Zoster.**—RUGGLES (*Arch. Dermat. and Syph.*, 1931, 23, 472) reports 15 cases of herpes zoster favorably influenced by the intravenous administration of sodium iodid in 2-gm. doses in 20 cc. of sterile water, given on the first, second, fourth and seventh day of observation. The early relief from pain and rapid involution of the skin lesions are quite striking in a number of the cases. The author claims no originality for the method and can advance no satisfactory explanation of its rationale, but offers it as a distinctly valuable addition to the therapy of extensive painful cases of zoster.

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**Cutaneous and Mucosal Relapse in Early Syphilis and Its Differentiation from Reinfection.**—STOKES, COLE, MOORE, O'LEARY, PARRAN and WILE (*Ven. Dis. Inform.*, 1931, 12, 55) have studied 5952 cases of early syphilis from their five respective clinics to ascertain the frequency, infectiousness, time and appearance, localization and morphology of relapse. Three hundred and sixty cases of mucocutaneous relapse and 40 supposed reinfections were thus brought to light, showing that relapse is one-fifth as frequent as chancre and reinfection one-ninth as prevalent as mucocutaneous relapse. The public health import of these facts is evident when one realizes that relapse is less conspicuous than chancre and consequently more easily ignored by patient and contact. Some of the more important conclusions of the paper are as follows: (1) The proportion of relapse is less in cases seropositive in the primary stage at the onset of treatment or in florid secondaries when they began treatment in the first year of their disease than in cases which are seronegative at the outset; (2) 68.6 per cent of mucocutaneous relapse was extragenital and 31.4 genital; (3) 62 per cent of relapse lesions are potentially infectious; (4) mucocutaneous relapse appears (91 per cent) in the first 2 years after treatment and 85 per cent of it occurs in the first 2 years of the disease; (5) arsphenamin-mercure therapy is followed by 9.6 per cent of relapse as compared with 3.6 per cent under arsphenamin-bismuth therapy; (6) the proportion of mucocutaneous relapse is greatly reduced after the ninth to the fifteenth arsphenamin injection; (7) the criteria for the acceptance of reinfection are reviewed and none in the present supposed series of reinfections are found to be completely acceptable. A small proportion only satisfy even moderately strict requirements.

## GYNECOLOGY AND OBSTETRICS

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**Roentgen Therapy of Uterine Cancer.**—At the Erlangen Roentgen Institute between 1915 and 1925 there were 956 cases of uterine cancer treated with Roentgen rays which are analyzed in a paper presented by WINTZ (*Ann. Surg.*, 1931, 93, 428). The treatment was based on the principle of applying the cancer dose, if possible, at one sitting or in the course of 48 hours. The results of treatment show that in carcinoma of the cervix there were 125 operable cases with 60 per cent 5-year cures and 712 inoperable cases with 12 per cent 5-year cures. Of the adenocarcinomas of the corpus there were 59 operable cases with 69.5 per cent 5-year cures and 160 inoperable cases with 8.3 per cent 5-year cures. Since 1921 the statistics have been even better than those mentioned, due largely to the use of copper treatment which produces secondary radiation in the tissues by metallic particles introduced by means of iontophoresis. He describes in detail the technique of this procedure. One of the reasons that this copper treatment has improved the results is that it accomplishes a deep disinfection of the tissues and it is well known that infected tissues do not respond to irradiation nearly so readily as comparatively uninfected tissues. He points out the importance of living conditions and systematic after care in patients treated by irradiation. In comparing two series of cases he found that of those in good circumstances 46 per cent were cured whereas of those in poor circumstances only 32 per cent were cured. The after care of these patients must aid the body to eliminate the products of degeneration. Mechanical cleansing is obtained by disinfecting irrigations. For those masses of decayed cells which have been swept off by the blood stream, sulphur is administered by mouth or intravenously. If the systemic condition is poor, arsenical preparations are used. The effect of altitude in accelerating metabolism is used to assist in eliminating degenerative products.

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**Early Diagnosis of Cervical Cancer.**—Several years ago we called attention to a new method developed by Schiller for the early detection of cancer of the cervix which was based upon the application of an iodine solution to the suspected cervix. He showed that normal tissues took the iodine stain whereas diseased tissues remained iodine negative. However, we are careful to state that all iodine negative tissues were not carcinomatous but were to be regarded as suspicious. This phenomenon was explained as being due to a deficiency in the glycogen content of atypical proliferating epithelial cells. This subject has been investigated by ISSACHANOW (*Zentralbl. f. Gyn.*, 1931, 55,

1215) who believes that it has been of real assistance in the early diagnosis of cancer. By means of statistical tables he shows that he has been able to detect early carcinoma in more than twice as many cases by this method as by the simple biopsy without the use of the iodine stain. In the technique which he has followed the patient is given a vaginal douche after which a speculum is inserted and the cervix is dried with cotton and painted with a 5 per cent tincture of iodine. The major portion of the cervix will be stained brown but in the suspicious cases there will be clear points (iodine negative) within this dark-brown field. This part of the field is either curetted away or removed by excision, taking some of the apparently healthy tissue with it. If a suspicious polyp be present, it is drawn down by forceps and removed at the base, being careful to get beyond the pedicle. The suspicious tissues are then examined microscopically for the final diagnosis. It would seem that by the use of this method as a routine many early cases would be detected which otherwise might not be regarded serious enough to demand a biopsy. (This is a valuable adjunct to the diagnosis of cervical cancer, but as pointed out by Issachanow it is by no means a substitute for the histologic method. One of the difficulties sometimes associated with biopsy is making certain that the tissue has been secured from the proper area and for this reason trachelectomy is preferable in certain cases. C. C. N.)

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## OPHTHALMOLOGY

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**Arcus Senilis as an Accompaniment of Cardiovascular Disease.**—SCOTT (*South. Med. J.*, 1931, 2, 24, 165) observed arcus senilis in 179 (6.2 per cent). Histologically, arcus senilis is a deposit of fatty substances and perhaps, also, of lime and hyalin particles in the corneal parenchyma. It occurs usually coincident with other changes indicative of old age, but it may appear even in childhood. Of 2891 patients of all ages examined in a cardiac clinic 63 per cent were white and 36 per cent colored, but of the arcus senilis cases 107 (59 per cent) were colored. One hundred and fifty-two of 780 patients with arteriosclerosis in some form showed definite arcus senilis (19 per cent). Thus, 84 per cent of the cases of arcus senilis were subject to arteriosclerotic changes and only 4 per cent showed no signs of cardiovascular disease. Of the arcus senilis cases 48 per cent belonged to the laboring class; the ages varied from 31 to 95 years and 64 per cent were between the

ages of 51 and 70 years. The frequency and predominance of arcus senilis among colored people is striking. Arteriosclerosis is quite commonly associated with this form of corneal degeneration and may be an etiologic factor; but the majority of arteriosclerotic patients do not have arcus senilis. Faulty nutrition and physical degeneration within an ethnic group may explain its frequency in negroes. Arcus senilis may then be looked upon as one of the indices of racial degeneration.

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## OTO-RHINO-LARYNGOLOGY

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UNDER THE CHARGE OF

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**The Value of the Schilling Hemogram in the Otologic Infections.**—In a detailed account of observations made on 9 cases ALDEN and DE MORRE (*Ann. Otol., Rhinol. and Laryngol.*, 1931, 40, 95) feel that the consistent manner in which the hemogram findings have paralleled the clinical features makes this laboratory aid of distinct value in the study of the otologic infections. Further confirmation is given in the fact that the stab cell count offers a much more reliable index of the patient's condition than does the polymorphonuclear percentage of the total number of the white blood cells, and particularly in children, than the pulse and temperature variations. The hemogram must be considered as a distinct advance in the interpretation of various blood findings, but cannot be expected to accurately differentiate between such closely allied conditions as acute suppurative otitis media and acute suppurative mastoiditis. It is also of far more value when daily or very frequent observations can be made under a strict set of conditions. It is by no means introduced to supplant clinical investigation, but to corroborate it. Finally, the correct valuation of such laboratory criteria permits an individualization of treatment according to the given case, because it furnishes data so significant as to make pathologic details more comprehensible and the results more uniformly successful.

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**Allergy in the Middle and the Internal Ear.**—In these days when hypersensitiveness is in the saddle many interesting and important phenomena are being encountered. PROETZ (*Ann. Otol., Rhinol. and Laryngol.*, 1931, 40, 67), after a bibliographic review and a clinical study of a limited series of cases, concludes that localized allergic reactions may simulate other aural diseases by the mechanical reactions of edema upon the tissues of the tympanum and labyrinth. They may be differentiated by the nature of the onset, often accompanied by allergic manifestations elsewhere by a careful history of the patient's sensitivities, and sometimes by the occurrence of eosinophilia.

**Histopathology and Bacteriology of Sinusitis: With Comments on Postoperative Repair.**—Based on a study of tissues secured from 15 persons, KISTNER (*Arch. Otolaryngol.*, 1931, 13, 225) noted epithelial or connective-tissue hyperplasia as a common structural change of the mucosa in chronic latent or nonpurulent sinusitis—regardless of the underlying etiologic factor, bacterial, allergic or avitaminosis. Pathogenic microorganisms were found in the tissues of those cases where the sinusitis was associated with systemic disease. The sinus and nasal mucous membranes differ greatly in histologic structure, organization and appearance. After complete destruction the sinus mucosa does not regenerate its structures. Granulation tissue organizing into typical scar tissue and bone proliferation are basic features of the reparative process. The type of epithelium which eventually covers the fibrous tissue depends on the character of and distance from the ancestral epithelium. Cultures from 400 sinuses usually yielded a mixture of organisms. Streptococci predominated (94.5 per cent). In the order of frequency, staphylococci, *Micrococcus catarrhalis*, pneumococci, *Bacillus Friedländer*, *Bacillus influenzae*, *Bacillus coli*, diphtheroids and streptothrix were found.

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## RADIOLOGY

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**Roentgen Treatment of Metastasis to the Vertebrae and the Bones of the Pelvis from Carcinoma of the Breast.**—Metastasis from carcinoma of the breast reaches the pelvic and vertebral bones probably by a combination of aberrant and reflux spreads through the lymphatics and is often accompanied by an inflammatory reaction of noninfectious origin, in the opinion of LEDDY (*Am. J. Roent. and Rad. Therap.*, 1930, 24, 657). The most common symptom of such lesions is pain in the right sciatic nerve. The distribution and type of metastasis, in the group of 40 cases studied by Leddy, have no relationship to the primary tumor. Treatment by Roentgen rays, by an effect on both the inflammatory and malignant cells in the metastatic growths, produces analgesia, often complete and of month's duration, and is the best method of palliating a hopeless case. But sooner or later Roentgen therapy loses its initial effectiveness. Usually one or two recurrences of symptoms due to reactivation of the metastasis in bone may be handled successfully, but eventually all treatment is useless.

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**Roentgen-Physiologic Studies of the Gall Bladder in Dogs.**—REWBIDGE and HALPERT (*Am. J. Roent. and Rad. Therap.*, 1930, 24, 634) injected lipiodol or brominol into the gall bladders of 26 healthy dogs

after laparotomy, and made cholecystograms at intervals thereafter. The shadow of the gall bladder disappeared in most of them in from two to seventeen days, but, in 5 dogs the shadow persisted with little change until the experiment ceased. At necropsy, droplets of lipiodol or brominol were found in the gall bladder of most of the dogs in which the shadow has disappeared. From these observations the writers conclude that complete emptying of the gall bladder does not occur with each meal; furthermore they regard it as probable that complete evacuation of the biliary vesicle never takes place in the dog.

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**Mixed Tumors of the Parotid Gland.**—These tumors of the parotid are usually mildly malignant new growths and are occasionally found in the other salivary glands or elsewhere about the face. The consensus of surgical opinion apparently favors early and radical removal of encapsulated tumors, but opposes attempts at removal of nonencapsulated growths. However, MERRITT (*Am. J. Roent. and Rad. Therap.*, 1931, 25, 507), who has treated 10 cases by radiologic methods, believes that the treatment should be in the hands of the radiologist. He considers that high-voltage Roentgen therapy is a useful adjunct to radium. While a small encapsulated tumor may be successfully excised, the author believes from the accumulated evidence that implanted radium will accomplish equally good results. He considers a combination of surgical removal with irradiation by either radium or Roentgen ray as illogical; if the former is adequate, the latter is superfluous. Failure to destroy the tumor by irradiation at the initial attempt does not induce the increased malignancy which frequently follows inadequate surgical treatment.

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**Influence of Ultraviolet Light on the Glucose Tolerance of Rabbits.**—Apparently little is known concerning the relation of ultraviolet light to glucose tolerances, and opposite views are held as to the effect of the former on the latter. ROOT (*Arch. Phys. Therap. X-ray, Rad.*, 1931, 12, 153) exposed a number of normal rabbits to irradiation with a quartz lamp for periods of 10 to 25 minutes, and the results of his investigations indicated that the ultraviolet light increases tolerance for high concentrations of glucose, although the mechanism of the action remains to be determined.

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**The Cavity in Pulmonary Tuberculosis.**—From roentgenologic studies at the Detroit Tuberculosis Sanitarium, PINNER and PARKER (*Am. J. Roentgenol. and Rad. Therap.*, 1931, 25, 454) have developed a classification of tuberculosis cavities in the lungs which they consider an important factor in prognosis and the selection of treatment. The first type is described roentgenologically as "moth-eaten areas in infiltrated parenchyma," the appearance being due to multiple small cavities without walls. These cavities are young, so to speak, and respond readily either to artificial pneumothorax or phrenectomy. The second type comprises the round or oval cavities with a definite, fibrous wall of varying thickness. These also are relatively young, and more than 60 per cent of them will close after phrenicotomy or

pneumothorax. The third type consists of large irregularly shaped cavities, with very thick walls. About one-half of them decrease in size under appropriate nonsurgical treatment; less than one-half are diminished by phrenicotomy or pneumothorax, and none close after such treatment. In short, therapeutic success in the surgical treatment of cavities is in inverse ratio to the amount of demonstrable fibrosis in the cavity walls.

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**The Present Status of Electrocoagulation of Tonsils.**—The relative advantages and disadvantages of surgical removal and electrocoagulation are compared by NOVAK (*Arch. Phys. Therap., X-ray, Rad.*, 1931, 12, 226). He arrives at the conclusion that, although surgical removal is not an ideal technique, in that it is liable to difficulties and complications, it is at present the best available technique. The removal of tonsils by diathermy is not devoid of risks, and the proper technique is not easy to learn or execute. A properly executed surgical tonsillectomy is a neat, swift, complete, workmanlike job in the ordinary case. Under similar conditions, diathermic destruction is slower, lacking in the precision and control characteristic of good surgery, and there is always the unpredictable factor of the depth of penetration obtained. Nevertheless, electrocoagulation has its place as an adjunctive method, and is the operation of choice in certain selected cases, especially those which are poor operative risks.

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**The Practical Value of Radium in the Treatment of Certain Fibroid Tumors of the Uterus.**—From his experience with 286 cases treated by intrauterine application of radium, after diagnostic curettage in all save 2, CRUTCHFIELD (*Radiol. Rev.*, 1931, 53, 89) is of the opinion that this treatment is the method of choice in menorrhagia associated with uncomplicated fibromyomata less in size than 3½ months' pregnancy in women approaching or within the menopause. On the other hand, radium treatment is contraindicated when the tumors are larger than a 3 months' pregnant uterus; when they are complicated by lesions on the adnexa; when they produce pain or other symptoms from pressure on the bladder or bloodvessels; when they are causing cachexia by necrosis; when the tumors are increasing rapidly in size or undergoing calcareous change; when the patients are under 35 years of age; when the fibroids are associated with other intraabdominal lesions; when the patient has an ineradicable fear of cancer; when the diagnosis is not clear. For all such cases surgical treatment is preferable.

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**Evaluation of Electrosurgery of the Tonsils.**—In the opinion of BALMER (*Arch. Phys. Ther., X-ray, Rad.*, 1931, 12, 10) electrocoagulation is the superior method for removal of postoperative tonsillar tissue and adhesions, lingual hypertrophy and varix, and for the extirpation of the faucial tonsil in the presence of certain diseases, such as hemophilia, anemia and the serious affections of the lung, heart and kidney. It is not applicable to children or to nervous or refractory patients. No method of tonsil removal is ideal under all circumstances, but the combination of surgery and electrocoagulation is a means of approaching the ideal.



## NEUROLOGY AND PSYCHIATRY

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**The Treatment of Postencephalitic Children in a Hospital School.**—BOND and APPEL (*Am. J. Psychiat.*, 1931, 10, 815) present an encouraging study of the treatment of 48 postencephalitic children in a hospital school. There were 14 controls in the group, bringing the total number of children presented to 62. The results they tabulated as follows:

	Post- encephalitic.	Controls.
Good . . . . .	7	1
Doubtful . . . . .	7	1
Poor . . . . .	6	2
Still in classes . . . . .	22	8
Feeble-minded . . . . .	6	2

They remark that "these figures show that in 20 postencephalitic (excluding the feeble-minded) sent home 7 had good results, or 35 per cent, as compared with the total failure of family placement, as reported by Healy." In this paper the authors describe in a general way the manner in which their work was carried out, noting that more detailed reports of various phases of the work would be reported later. The hospital school in which the work was done possessed adequate living quarters and recreational facilities, and was connected with separate men's and women's departments of the Pennsylvania Hospital for Mental and Nervous Diseases. The personnel of this institution consisted of: A nurse in charge trained in psychiatric nursing; graduate and student relief nurses; occasional attendants; male nurses with the boys and female nurses with the girls; a teacher, trained in special class-work, had charge of their schoolwork; occupational therapy teachers had charge of the children part of the time that they were not in school. Regular periods for a singing class were held by a music teacher. A psychologist made tests from time to time. The gymnasium and swimming pool were adequately supervised. Several psychiatrists who has special interests in children supervised and coördinated the work. The routine of the day, while not absolutely rigid, followed certain regular lines. This, it was found, eliminated much of the mischief through substitutive activity. A certain amount of free playtime was found necessary. In addition, the authors note, impersonal schedules and gross group methods were not enough—that individualizations and consideration of the separate personalities had to be added to obtain the best results. With this background to work with, the authors state that "The psychiatric nurse, trained to look upon unusual irritating and antisocial behavior with equanimity and understanding, was a

great help. The children thus found no unemotional background to their behavior in the hospital, which was in marked contrast to what they had experienced before hospital entry. . . . The children were encouraged to feel that their behavior difficulties could be cured like any other conditions for which one enters the hospital. . . . Graded schoolwork was carried on, but emphasis naturally had to be placed on individual difficulties and problems. The amount of work done was probably equal to one-half or two-thirds of that done in the ordinary grade school. The group lacked initiative and originality notwithstanding their restlessness and curiosity." The hospital point of view and plan was continuously emphasized. The workers were urged to read various books on the problems of children in order that they might understand the problems of those with whom they came in contact. A definite attempt was made to have all exhibit a spirit of optimism. An unemotional attitude toward delinquency was developed. The workers were requested to maintain an attitude of impersonal authority, and understanding and coöperation were stressed rather than criticism, discipline and punishment. In order to bring home to those in charge of the children that behavior disorders are the manifestations of difficulties in the dynamics of personality adjustments, conferences were held at varying intervals. All attended—then observations, impressions and suggestions were pooled in order that no conflicting attitudes on the part of the workers might exist. Concrete accounts of the activities of the children were then related and a general discussion of the outstanding traits or greatest problems and the best approach to the problem would conclude the conference. The authors found that "There are objections to such a formal procedure, but it gave a *modus operandi* to get all the personnel thinking on the child's personality and its problems, and his reactions in terms of his needs."

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**Encephalitis and Encephalomyelitis in Measles.**—TERRARO and SCHEFFER (*Arch. Neurol. and Psychiat.*, 1931, 25, 748) report 6 cases of measles that died of central nervous system complications. These cases are presented in detail, each giving an adequate clinical summary and a very complete pathologic report. The histopathologic studies of the cases which form the major portion of the paper show that in all 6 cases the lesions of the brain were practically the same. They consisted mainly of a perivascular proliferation, formed especially of microglial elements. The microglial nature of the cell was brought out by the specific methods of silver impregnation. In some instances there were scattered elements of hematogenous nature in the perivascular areas. These elements were mainly lymphocytes and occasionally plasma cells. The perivascular hematogenous elements were "never of great importance and in some cases there was no trace of them in all the material studied." The perivascular proliferation was dominantly located in the white substance, where it formed large islands. The cortex, however, was involved by the same process, although to a much less extent. Accompanying the perivascular proliferation there was demyelination, which formed another characteristic of the pathologic process. Lesions involving the axis cylinders in the demyelinated areas were also noted. Less characteristic was the macroglial reaction,

with both its progressive and its regressive changes. In addition, the authors point out a frequency of thrombi (red thrombi) and the occurrence of vascular changes, swelling or hyperplasia of the endothelium. This latter finding, they state, points "to a participation of the vascular system in the process, and this fact, associated with the one that most of the lesions are perivascular in topography, justifies the hypothesis that whatever noxious agent is the cause of the lesions, this agent is carried from the bloodvessels to the surrounding tissue and is favored by an abnormal permeability of the protective wall and stasis of the venous system." In addition, the authors present the three main views of the etiology of encephalitis that follows vaccinations or acute exanthematous diseases: "(1) That the lesions in the brain and cord are due directly to the action of the virus of smallpox, vaccinia or measles; (2) that they represent an allergic or anaphylactic phenomenon occasioned by the preceding illness; (3) that they are caused by an unknown virus or toxin which is in some way empowered by the exanthematous disease to attack the nervous system." They present the proof both for and against these theories and finally conclude that: "In the present state of knowledge it seems to us that acute disseminated encephalomyelitis is most likely a toxic reaction of the central nervous system occurring in a number of different virus conditions."

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## PATHOLOGY AND BACTERIOLOGY

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**The Titration of Scarlatinal Antitoxin by Means of a Skin Test in Chinchilla Rabbits.**—FRASER and PLUMMER (*Brit. J. Exp. Path.*, 1930, 11, 291) describes a method for the titration of scarlatinal antitoxin which is suitable at least for preliminary testing. Chinchilla rabbits were used and the skin tests were carried out just as in the human skin test. The test dose of toxin used was eight to ten times that of the human test dose, and this was added to an equal quantity of the various dilutions of antitoxin. The tests were measured at the end of 24 and 48 hours after injection. In a series of carefully controlled experiments it was found that the accuracy of the skin titration in rabbits was within similar if not identical limits to that in human subjects, provided that one-half as many more animal tests are done. This necessity for a greater number of tests in rabbits was due to a greater dispersion in the readings. Two antitoxins could be distinguished if one were at least twice as strong as the other, and in 2 cases out of 3 this was possible if one toxin were only one and a half times as strong as the other.

**Anatomical Characteristics of Tuberculosis in Jamaica.**—OPIE (*Am. Rev. Tuberc.*, 1930, 22, 613) has reported upon 9 fatal cases of pulmonary tuberculosis in Jamaican adults, a large proportion of which had the characters of tuberculosis occurring in infancy and early childhood among people of European origin. Five cases were of this type, and in them the lesions had their origin in the lower lobes of the lungs, while the apices were either not involved or contained inconspicuous lesions. In 3 instances there was widespread tuberculous bronchopneumonia throughout the lungs with massive tuberculous of tracheobronchial lymph nodes. In the fourth case the disease had made little progress in the lung, but there was massive tuberculous of the tracheobronchial lymph nodes and death occurred from acute miliary tuberculosis. In the fifth instance the lesions in lung and lymph nodes were similar to those seen in the other 4, but there was also caseation of mesenteric lymph nodes. In all of these autopsies careful dissection failed to reveal any scars of preceding tuberculous, and the lesions of lung and lymph nodes had all the characters of first infections. Of the remaining 4 cases the tuberculous lesions apparently had their origins in the apices of the lung, and in this respect resembled the tuberculosis of white adults. One case, however, was otherwise of childhood type, and was apparently a first infection. In 2 cases the lesions were intermediate between those typical of childhood and adult infections, while the last case showed a pulmonary tuberculous similar to that usually seen in white adults.

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**Pulmonary Asbestosis. A Report of a Case and a Review.**—SOPER (*Am. Rev. Tuberc.*, 1930, 22, 571) has reported a case clinically typical of pulmonary asbestosis. The patient had a history of exposure to asbestos dust for 12 years. The first symptoms of the disease appeared about 6 months prior to admission to hospital in the form of increasing dyspnea, malaise and loss of weight. He had a small amount of sputum, sometimes streaked with blood. Physical examination of the chest showed signs of bilateral pulmonary fibrosis. A few dry, crackling râles were heard at the bases about the whole circumference of the chest. These were also audible here and there over the whole chest. The outstanding feature of Roentgen ray plates of the chest was a diffuse fine type of shadowing, which, about the hilum of both lungs and about the bases, presented a "cobweb" appearance. Pathologic examination was not obtained in this case, but typically pleural adhesions are extensive, the lungs are firm and fibrotic, and the bronchi may be dilated with extensive peribronchial fibrosis. In addition, certain "golden yellow bodies," characteristic of the disease, may be expressed from the cut surface of the lung. These have been aptly called "asbestosis bodies." They may be shown to contain in their centers cores of asbestos fibers. Asbestos contains only a very small amount of free silica, but in the opinion of the author it probably conduces to a more rapid development of any concomitant tuberculous, as in the better understood forms of silicosis.

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**Tuberculosis of the Liver.**—MORRIS (*Am. Rev. Tuberc.*, 1930, 22, 585) reports a case of tuberculous of the liver in a man, aged 58 years, who had an advanced tuberculous lesion in the upper lobes of both

lungs with cavitation in the right upper lobe. Apart from the usual symptoms of terminal pulmonary tuberculosis, the patient presented more severe ones referable to the intestinal tract, all of which were attributed to intestinal tuberculosis. On physical examination the liver was slightly enlarged and tender on pressure. At autopsy the liver was found to be greatly enlarged with numerous large, hard, yellow nodular areas over the entire surface. These areas were filled with caseous material enclosed in fibrous capsules, varying from  $\frac{1}{2}$  to 1 inch in diameter. Such cases of localized tuberculosis of the liver are rare and have never been diagnosed except by laparotomy. Miliary tuberculosis of the liver is found quite commonly in cases dying from pulmonary tuberculosis, but is quite uncommon without generalized tuberculosis. RANDOLPH (*Am. Rev. Tuberc.*, 1930, 22, 593) reports a case, however, in which there were no clinical signs of pulmonary tuberculosis, and Roentgen ray of the chest gave no suggestion of pulmonary lesion. The onset of the illness was acute with chills and fever and an irregular fever continued, ranging from 101° to 104° F. At the onset the liver was slightly enlarged, but increased in size from day to day, and from the ninth to the twelfth day with great rapidity. Fourteen days after the onset laparotomy was undertaken with a view to draining a possible abscess. The patient died on the following day. At autopsy the liver was found to be greatly enlarged with discrete scarring of the surface which proved to be due to a portal cirrhosis. Numerous small, grayish-white nodules were scattered through the liver, and these were found on microscopic examination to be miliary tubercles of recent origin and all at about the same stage of development. Spleen and kidneys showed no tuberculosis. The explanation was offered that an old abdominal focus of tuberculosis had become active and seeded the liver through the portal circulation.

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## HYGIENE AND PUBLIC HEALTH

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UNDER THE CHARGE OF

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**An Unusually Mild Recurring Epidemic Simulating Food Infection.**—SPENCER (*Pub. Health Rep.*, 1930, 45, 2867) reports on the remarkable condition occurring periodically in the mountainous parts of the West, particularly in the National Parks. The onset is sudden and violent, with nausea, vomiting, sharp pains in the abdomen and diarrhea. In a few hours the attack was over and the patient well except for weak-

ness. The condition could not be associated with any particular item of food or water from any particular source. There was definite leukocytosis. Cultural studies and serologic tests gave no suggestive findings.

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**A Study of the Effect of Typhoid Vaccine When Given After Infection.**—CROUCH (*U. S. Pub. Health Rep.*, 1930, 45, 2429) presents data which would seem to justify the tentative conclusion that typhoid vaccine is well worth while when given after the infection is received, provided the first dose is given before the onset of symptoms and provided further that three doses are given. Typhoid vaccine when given soon after the onset of symptoms is of little or no benefit.

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**Mottled Enamel in a Segregated Population.**—KEMPFF and MCKAY (*U. S. Pub. Health Rep.*, 1930, 45, 2923) review the history of this condition of the teeth and emphasize the high frequency of the discoloration in areas where it prevails. Cuts illustrate the disfiguring nature of the condition. Permanent teeth alone are involved. The condition in the community under study coincided with the introduction of deep well water. The data point to rather exact localization of mottled teeth and proved a relation to the water supply, but the exact fault of the water has not been determined.

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**The Typhus-Rocky Mountain Spotted Fever Group. An Epidemiological and Clinical Study in the Eastern and Southeastern States.**—RUMREICH, DYER and BADGER (*Pub. Health Rep.*, 1931, 46, 470) have separated certain eruptive diseases occurring in the eastern seaboard states into two clinical entities; one of these is endemic typhus of the type previously described by Brill, Maxcy, and others, the other a virus infection of the Rocky Mountain spotted fever type. There is an important difference between the two in that the latter group of cases have a definite mortality somewhere in the neighborhood of 20 per cent, whereas the typhus cases are practically without fatalities. The onset is very similar in the two, but the duration of the fever in the typhus cases is apt to be cut short by a crisis on the fourteenth or fifteenth day, while it may be either shorter or longer in the spotted fever group of cases. The distribution of rash is also different, in the typhus cases beginning on the thorax and abdomen, spreading later to the arms and legs and rarely involving the face, whereas in the spotted fever group of cases the extremities are involved first and the face usually is implicated. The seasonal distribution is substantially similar and there is a strong suggestion on epidemiological grounds that the Rocky Mountain spotted fever cases are tick-borne, while the suggestion, perhaps not quite so strong, is that the typhus cases might have been infected from fleas.

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**Undulant Fever. With Special Reference to a Study of Brucella Infection in Iowa.**—HARDY and his associates (*U. S. Pub. Health Rep.*, 1930, 45, 2433, 2525) discuss the subject at length. The epidemiologic part of their studies is summarized as follows: Undulant fever due to

infection with the abortus or suis varieties of *Br. melitensis* is wide spread, and in regions in which systematic investigations have been conducted the disease has been found to be of not infrequent occurrence. It has involved chiefly young and middle-aged adults, and males have predominated in all but very few studies. Men on the farms and packing-house employees have been particularly involved. Cattle have been generally regarded as the source of human infection, but in some localities hogs have played an important part. That direct contact with animals often accounts for human infection is being more generally recognized. Evidence indicates that the skin may be an important portal of entry. Otero, of Porto Rico, in a personal communication, writes as follows concerning his experiments on human volunteers: "It may be of interest to know that some of our inoculations, through abraded skin have been successful, giving rise to clear-cut cases of undulant fever after a single inoculation, in some cases with strains that were fed repeatedly with apparently no symptoms. I have 6 such cases at present running fever." The authors feel that the date presented make untenable the opinion that the ingestion of raw dairy products from infected cows is the only means of transmission of undulant fever. It is apparent, in Iowa, at least, that approximately one-half of the cases result from a second means of transmission, namely, through contact with infected animals, their tissues, or discharges; the infection in all probability entering through the skin. The section on Prevention deserves special attention. The important parts may be summarized as follows: Vaccination with killed cultures is valueless. Proper pasteurization of milk renders the fluid safe. The agglutination test is recommended to be applied to cattle to enable the owners to eliminate infected animals. The ultimate control of the condition lies with the veterinary profession.

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ORIGINAL ARTICLES.

PROBLEMS OF PRESENT-DAY GASTROENTEROLOGY.\*

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In my estimation the greatest problem that still faces the gastroenterologist is: Why does food go aborally down the bowel? Until the mechanism which normally keeps waves traveling down the stomach and bowel is known and thoroughly understood the physician must always feel somewhat embarrassed when he is asked to overcome dynamic or paralytic ileus, or when he is asked to stop nausea, regurgitation or vomiting; it must be obvious that one cannot hope to tinker successfully at a mechanism, the normal functioning of which he does not fully understand.

**Problems of Physiology. Gradients.** It now appears probable that peristaltic waves tend to travel aborally largely because the upper part of the bowel is more active, more irritable, and more responsive to every stimulus than is the lower part. Since the tonus and activity of the intestinal wall decrease gradually from duodenum to colon, it can be said that food follows a gradient of force similar to the one which causes oil to flow along a pipe line. This gradient of force in the bowel might conceivably be reversed if the muscle in the lower end of the bowel were to become irritated, as by inflammation, until it became as active and tonic as the muscle in the upper end usually is; and actually, Hosoi and I have produced such reversal in animals by injecting irritant substances into the tissues about the ileocecal sphincter. As we expected in these animals, the small

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bowel often showed an inability to forward its contents; the local rhythmic movements were active enough, but the big traveling waves were hard to start, and when they did appear they traveled slowly and soon tended to fade out.

The gradient of force might also be reversed by the action of any poison that would injure the highly sensitive neuromuscular apparatus in the upper end of the bowel more than it would injure the less sensitive mechanism in the lower end. I think it probable that this is one of the ways in which some drugs produce nausea, and in which fatigue, exhaustion and infectious diseases upset digestion. As is well known, a man or woman who is coming down with a cold or who is suffering from tuberculosis loses appetite, and a dog with distemper refuses to eat. If the dog is fed forcibly the food will not leave the stomach, although there is no obstruction at the pylorus, and if one studies the intestinal gradient in such an animal it will often be found reversed. Hysterical women and frail weak girls often seem to have such a poor gradient of forces in the bowel that it is hard for them to get any food through in the normal direction but it is easy enough for them to pass it back the wrong way.

It is unfortunate that as yet we gastroenterologists are without any drug that can be counted on to steepen or to restore to normal these reversed gradients, and hence we have to get along as best we can with prescriptions for good hygiene, rest, tonic measures, and outdoor life. Surely, it will be a great day for us when someone discovers a drug that will always stop nausea and regurgitation and vomiting, and will make it possible for frail, neurotic, and exhausted women to eat with appetite and zest.

A few years ago Hosoi and I showed, as we had hoped to do, that the gradient of irritability down the bowel is commonly reversed in pregnant animals. This reversal seems to be due to an increase in the metabolic activity of the lower part of the bowel, an increase which is shared by most of the tissues in the neighborhood of the growing uterus. It now seems probable that a reversal of the gradient of forces in the bowel can be produced by any agency that will depress the functions of sensitiveness and activity more in the upper part of the bowel than in the lower part, or which will stimulate them in the lower part more than in the upper.

A theory becomes a valuable working hypothesis when it seems to explain and throw light on many facts of observation, and actually, the gradient idea offers we practising physicians and surgeons the only explanation we now have for many of those peculiarities of intestinal activity which we see in our daily work. It has also been helpful in suggesting useful therapeutic maneuvers. Thus, it can easily be seen that a digestive tract in which the forces are somewhat reversed is likely to work better if solid food is put into the stomach. The presence of such food will tend to increase the tonus of the muscle in the upper end of the tract and the gradient down the

bowel will thereby be steepened. On the other hand, the putting of irritant material into the rectum, especially after operations on the pelvic organs, should tend still further to reverse an upset gradient, and thus cause vomiting. Actually, surgeons have found after operations that the Murphy drip, if used to excess, will cause nausea and other discomforts.

It may be that one of the reasons why calomel works so well in some "bilious" persons is that it steepens the gradient of forces in the bowel and causes the current to set downward and not upward. This, of course, is pure conjecture, because, so far as I know, no one has studied the influence of calomel on the intestinal gradients.

*The Nerves of the Tract.* Although much of value has been learned about the various related gradients and the ways in which they can help to maintain the normal direction of peristalsis, much remains to be learned about the structure and functions of Auerbach's plexus, and about the ways in which it mediates conduction along the bowel. The work of several investigators has shown that often, as after operations, when the bowel appears to be paralyzed the muscle remains quiet, not because it has been weakened by toxins, but because it is inhibited by nervous action. Thus, the intestinal muscle of a dog that is dying of peritonitis will contract rhythmically and normally if the splanchnic nerves are cut or if the bowel is excised and placed in warm oxygenated Locke's solution. One can see from this why it is that in some cases of dynamic ileus if nervous inhibition is removed by the induction of spinal anesthesia, the bowels will move immediately.

Some work which Hosoi and I did a few years ago on scores of rabbits convinced us that both the vagus and the splanchnic nerves serve largely as brakes to the bowel. Without these brakes the gut tends to respond to every stimulus, and the animals often die of diarrhea and inanition. This work, together with much else reported in the literature, left me strongly inclined to believe with Cannon that most of what has been written so convincingly about vagotonia and sympatheticotonia is wrong and without foundation in fact.

*Indigestion is Produced by Motor Dysfunction.* For the last 17 years I have felt so certain that gastroenterology is to advance only as more knowledge is secured in regard to the motor functions of the digestive tract, that I have been spending half of every day in a laboratory of physiology studying the movements of the stomach and bowel. To be sure, the secretory functions of the tract are also important and there is a great need for knowing more about them, but the symptoms of indigestion are, I believe, produced mainly by disturbances in the motor functions. As proof of this, I need only cite the fact that perhaps 1 of every 3 men and women, aged more than 60 years, is living fairly or quite comfortably with no free acid in the gastric juice. If, however, in one of these persons

there were to come a breakdown in the motor transport through pylorus or intestine, that man or woman would be forced, within a few hours or days, to consult a physician.

*Gastric Secretion.* It is sad to have to admit that after all the years spent in the study of gastric secretion our knowledge in regard to it remains elementary and insufficient. We physicians know a little about the concentration of hydrochloric acid in health and disease, but we cannot control it satisfactorily, and we still know almost nothing about the concentration of pepsin in various diseases. Worse yet, we do not know why the normal stomach does not digest itself and why the diseased one sometimes does. If Michaelis is right and the protection of living cells lies in the fact the lining membrane is made up of lipoids which are not digestible by pepsin, those investigators who are now searching for the cause of ulcer should be studying lipases and not hydrochloric acid.

*Flatulence.* There is much need for more knowledge in regard to the absorption of food residues and gases. It is known now that the gases which are being formed constantly in the bowel are normally being carried away by the blood stream and excreted through the lungs, but it is not yet known just how this mechanism is disturbed in persons who suffer with flatulence. It is even possible that in many cases it is not disturbed and that the offending gas is nitrogen, which represents the almost unabsorbable residue left from swallowed air. The next question is: Why do some persons swallow so much more air than others? The worst air swallower I ever watched back of the roentgenoscopic screen could get into his stomach perhaps 500 cc. of air while he was drinking a glass of milk, but neither he nor I could see wherein his method of swallowing was different from that of his more healthy fellows.

*Functional Disturbances of Digestion.* *Disturbances Due to Emotions.* The next big problem, which of course is but a continuation of the ones that I have just been outlining, is: What is the mechanism of the nervous or functional disturbances of digestion? Fortunately, there is now at hand some knowledge as to the ways in which emotion can affect the various functions of the digestive tract. Thus, it is known that mental distraction, fright, worry, disgust, or annoyance at mealtime can, for hours afterward, interfere with the emptying of the stomach. It is known also that these mental disturbances can either greatly delay or else markedly stimulate the movements of the bowel. Psychic upsets can also put a stop to digestion by drying up the various secretions that are normally poured into the various parts of the tract. The resulting failure of chemical digestion is followed by failure of absorption, and this produces irritation or inflammation of the mucous membrane of the bowel. This, again, produces more indigestion, and thus is started a vicious circle which can be broken only by careful dieting. Emotion can cause also blanching or blushing of the intes-

tinal mucosa much as it causes blanching and blushing of the skin, and such changes might account for disturbances in digestion and absorption. Everyone knows that anxiety and fright can cause diarrhea, and many physicians know that worry can cause constipation.

*Indigestion Originating in Constipation.* The presence of hard feces plugging the lower end of the colon will often lead to the accumulation of gas in the splenic flexure, and of feces in the cecum. The stagnation of foul material in the right side of the colon will in turn produce irritation and even actual typhlitis, and with this, there will be pain resembling that of appendicitis. In such cases, if the rectal plug can be removed gently, as by an enema of warm physiologic salt solution, all of the flatulence and pain and indigestion will be relieved.

*Effects of a Coarse Diet.* Many disturbances of digestion are doubtless due to the eating of rough irritant foods, poorly prepared foods, or foods to which the patient is sensitive. In such cases the prescription of a proper diet will bring relief, but in many others the most careful dieting will have little if any effect.

*Constitutional Inadequacy.* As already suggested in the first part of this article, many disturbances of digestion can best be explained on the assumption that the gradient of forces down the bowel has been flattened or reversed, perhaps by fatigue, exhaustion, nervous depression, or painful emotion. In many cases the primary defect seems to be a congenital or a hereditary one because several members of a family will complain all their lives of being easily fatigued, easily excited, and markedly disposed to suffer with headache, insomnia, and general nervousness. They appear to be constitutionally inadequate to stand the strain and stress of life. Thousands of these persons are now going from physician to physician in search of help; they constitute a large fraction of our clientele, and yet we often fail to recognize the underlying cause for their complaints. Instead of helping them to understand the true nature of their handicap, instead of teaching them that they must stop hunting for a complete cure, and instead of showing them how to live so as to get as much work as possible out of a defective piece of machinery, many of us put these patients through long and trying courses of examination and treatment; for weary months we "drain the gall bladder," we dilate hypothetical ureteral strictures, we treat hypothetical ulcers with Sippy cures, we remove teeth and tonsils, and sooner or later we explore the abdomen. Unfortunately, the more scientifically trained the physician, the more likely he is to offend against these poor patients because he knows of more things to do.

*Migraine.* Although migraine is, I think, a disease of the brain or of some phase of metabolism and not a disease of the digestive tract, it is of tremendous interest to the gastroenterologist because most of the patients with sick headaches go to him fully convinced that

if he would cure their digestive upsets they would be well. I am sorry to say that quite commonly physicians are so deceived by the presence of nausea, vomiting, and abdominal pain that the patient is put to the expense of one or more needless and useless operations.

Not infrequently, the symptoms suggest that cholecystitis may be present, but the wise clinician will continue to question the patient until he makes sure that there is never any indigestion between attacks and never an attack without the preliminary headache. He will know then, that the disease is not in the abdomen but probably in an irritable spot up in the brain from whence there spreads out down the vagus or splanchnic nerves a "storm" similar to that which produces the gastric crises of tabes or the vomiting of sea sickness. Even when gall stones are found their removal may have little if any effect on the course of the disease.

Recently a number of writers have come forward claiming that most cases of migraine are due to the eating of food to which the patient responds in an allergic way. I have seen a few cases in which headache did disappear after the elimination of certain foods, and I have found evidence of an allergic type of sensitiveness in many others, but my successes with dieting have been so few that I fear the cause of most cases of migraine has not yet been found. I think, however, that a promising lead has been opened and it should be followed out in every case with as much care as the intelligence and pertinacity of the individual patient will permit.

The difficulty is, that migraine is so often found in highly sensitive or distinctly neurotic persons who will not take good care of the brain; they work long hours, they pay little attention to the need for sleep, and in many ways they keep the cerebral cortex in such an irritable condition that many triggers here and there in the body will be able to start the attack.

There is evidence also that some of the attacks come at certain points in certain rhythmic cycles of metabolic activity which as yet are barely recognized and not at all understood. To me it has been suggestive that all of the research workers who have recorded daily the degree of activity of animals kept in cages have found remarkable cycles of increase and decrease. Some of these cycles are long and probably correspond to the menstrual cycle in women, while others have shorter periods. Already there is definite evidence that such cycles are present in men and women, and more must be learned about them.

It may be that knowledge in regard to these metabolic ups and downs and their mode of production will help later to explain the alternating cycles of well-being and of depression or feeling of toxicity which are seen in many psychopathic and otherwise constitutionally inadequate persons. Why is it that on some days they are full of energy and on others they wake up feeling weak and blue and unable to face the world and the work that they have to do?

*Constipation.* Reading the other day a translation of the Eber's Papyrus, a book which has come down to us from the time of the building of the Pyramids, I was struck by the fact that so large a number of these ancient prescriptions were designed for the relief of constipation. And here we are, 5000 years later, using some of the same drugs that are mentioned in that papyrus, and almost as ignorant as were the Egyptians in regard to the real causes of the disease. We physicians still must admit that in many cases there is no real or permanent cure for constipation. Even the bulky diets which are now so commonly used tend after a time to lose their efficacy just as laxatives do.

I have hopes that during the next decade some help will come from the neurosurgeon. He is now experimenting with sectioning of some of the nerves which produce spasm of the lower segment of the bowel, and something useful may come out of this work. It may be, also, that more of the patients with intractable constipation will be asked to submit to a transplantation of the terminal ileum to some point in the transverse colon. I see two main difficulties: one, that so many of the affected patients are too querulous and neurotic to be good subjects for any form of surgical intervention, and the other, that any operation for constipation which for a time seems to be very successful, later tends to lose its efficacy and the patient is back where he was before.

One helpful measure that I have discovered is the use of enemas of warm physiologic salt solution. In most cases of constipation the stagnation of feces is in the last few inches of the colon, and it would seem most logical to wash out this segment without upsetting and irritating the many feet of bowel up above. When one mentions an enema to many of these patients, they immediately say that the procedure has been tried and found unsatisfactory. These persons often have a very sensitive colon and if one tries to inject plain water or soapy water into it, there is much spasm and it may take hours of struggle to get the water in and then it may take hours to get it out. If, now, such a patient will put into the enema bag warm physiologic saline solution (a tablespoonful of table salt to 2 quarts of water) he or she will generally have no difficulty in getting it either in or out and there will be no irritation of the bowel and no passage of mucus afterward.

Physiologic salt solution will not irritate the mucous membrane of the colon and I cannot imagine how there could be any permanent injury. I believe, therefore, that physicians are not justified in warning patients as they now do against the frequent use of enemas. If many of the persons who now complain of flatulence and indigestion were only taught to remove, in this simple way, the fecal plug which obstructs the lower end of the bowel they would promptly get well.

*Diarrhea.* It is sad to have to admit that in many cases of diarrhea a definite diagnosis cannot be made. If examination of the stools does not show any sign of parasites, if the roentgenograms show a normally haustrated colon, and if the sigmoidoscopic examination shows a normal mucous membrane, the physician must feel more or less stumped. Diarrhea which comes only in the morning will sometimes be associated with achlorhydria, and in other cases it may be found that the attacks are due to excitement or worry.

Some types of diarrhea seem to be due to a familial predisposition; the stools may be loose for many years and yet the patient is not ill. In many other cases a cause cannot be found and, actually, I have seen a few persons who died of diarrhea and yet the pathologist was unable to say what had gone wrong with the digestive tract. Obviously, there is need for further research in this field. In this connection it may be interesting to note that in a large percentage of the experiments in which my assistants and I cut the splanchnic or vagus nerves in rabbits the animals died later of diarrhea and inanition; it seemed as if the brakes had been taken off the bowel.

It is conceivable, also, that in some cases of diarrhea something has gone wrong with the function of absorption. I can remember studying a young woman with a diarrhea which had been present off and on for years without inconveniencing her to any great extent. Roentgenologic examinations showed that the feces in the transverse, ascending and descending portions of the colon were normally desiccated and formed, and yet those that came from the rectum were soft and even watery. It seemed obvious, therefore, that something had gone wrong with the absorbing mechanism of the colon and that water was actually coming back from the blood into the sigmoidal and rectal segments. I mention this observation simply to show one way in which the problem of diarrhea will have to be studied.

**"Functional" Troubles that May Have an Organic Basis.** I have now offered explanations for the symptoms of a large number of patients in whom macroscopic lesions are rarely found at operation or necropsy. Unfortunately, there still remains a large number of persons who, while they do not seem to be suffering with any one of the few definite diseases which are known to occur in the abdomen, are yet too sensible and too severely incapacitated to be dismissed as "neuros." Many of these persons are seriously ill; their troubles perhaps came suddenly out of a clear sky; they are perhaps waking at night with distress, and perhaps they have already submitted to one or more exploratory operations. If they have not, the wise physician will not care to order one because he knows that, with the peculiar history and the sheaf of negative laboratory reports, it will probably be useless to open the abdomen.

What is wrong with these persons? My own impression is that many of them must have some lesion in the digestive tract or in its nerves and related ganglia, but what it is or where it is, I have but a faint idea.

*Gastritis and Enteritis.* In many of these cases some physicians tend to fall back on the diagnosis of "gastritis," but the available evidence indicates that this is not a common disease, and even if it were present, it is doubtful if it would always produce symptoms. I think it more probable that at times some form of enteritis is present, and experiments on animals have shown that inflammation in any part of the wall of the bowel will produce disturbances of digestion and will give rise to symptoms.

I feel sure that at times there is some form of inflammation in the region of the ileocecal sphincter which can produce a syndrome similar to that of chronic or recurrent appendicitis. To be sure, many of the patients who do not get well or who fail to stay well after appendectomy are neurotic or are suffering with duodenal ulcer, cholecystitis, mucous colitis, or constipation, but there are some who continue to suffer with symptoms that are typical of a smouldering appendicitis, and in them I feel sure that there must be some source of irritation in the ileocecal region.

Years ago I prophesied that some form of duodenitis would some day be found to account for symptoms and Roentgen ray findings closely resembling those of ulcer, and today it is a well-recognized disease. Similarly, I think it safe now to prophesy that several new diseases will be found along the course of the bowel when the pathologist takes time to look more closely for them.

*Hepatitis.* The presence of some degree of hepatitis is commonly noted during operations on the gall bladder, and I think it probable that it produces symptoms, and that in some cases it accounts for the postoperative persistence of a clinical picture that resembles that of cholecystitis. It has always seemed to me that when the surgeon removes a diseased gall bladder he must often leave behind in the liver much of the disease he was trying to cure. For this reason the wonder to me is not that he sometimes fails to relieve the symptoms but that he so often succeeds in doing so. Apparently, when the main focus of infection is removed, the other parts of the biliary system are better able to clear themselves of infection.

*Cirrhosis of the Liver.* It would seem that cirrhosis of the liver should, even in the earlier stages, produce some symptoms, and perhaps at times it does account for cases of severe, otherwise unexplainable, flatulence with soreness in the right upper quadrant. The objection to this theory is that occasionally one sees patients who have recovered from symptoms of cirrhosis and who continue to show a considerable degree of dye-retention with the Rowntree-Rosenthal test, but who do not suffer with any symptoms of indigestion. In other cases, when the physician is disappointed over his



failure to show the expected defect in liver function, he must admit that this probably does not mean much because the liver has many functions, most of them as yet unassayable, and all of them with such a large factor of safety that by the time a defect can be shown, the patient is about ready to die.

In spite of all these difficulties, I still feel that a clinical picture which resembles that of cholecystitis is probably often produced by a smouldering infection in the liver. Sometimes this infection will invade joints, sinuses, prostate, or heart. I believe, therefore, that one of the drugs that is most needed in gastroenterology today is one which will help the body in overcoming this smouldering type of septicemia.

*Pancreatitis.* One wonders, at times, if perhaps a mild pancreatitis might be present and responsible for vague distressing symptoms in the abdomen, and for pains shooting straight back into the spine or downward toward the hypogastrium. Against this theory is the fact that oftentimes at necropsy fairly severe pancreatic infection, destruction, or irritation, such as is produced by a perforating ulcer or by gall stones, will be found when the history had not led the physician to suspect its presence. In other words, the pancreas seems to be so poorly supplied with sensory nerves that it does not always complain when it is hurt.

Both with cirrhosis and pancreatitis the presence or absence of symptoms must, of course, depend partly on the degree of sensitiveness of the individual. As Libman has pointed out, the insensitive type of person will remain at work quite unconscious of illness long after some severe disease has begun to gnaw at his vitals.

*Mild Infection with Neurotropic Viruses.* A type of infection that I think can be held responsible for many poorly explainable "nervous breakdowns" is one with an encephalitic virus of low virulence. This is but a theory of mine but it is based on a number of observations. It is well known that in some laboratories almost every other supposedly normal rabbit is a carrier of the encephalitic virus, and I strongly suspect that some men and women are similarly affected. When the body resistance is lowered by some infection such as that of vaccinia or influenza, encephalitis will sometimes flare up in such a way that the conclusion must be that the virus was already present in the brain. Similarly, a cold will often bring on an attack of labial herpes, which is due to a neurotropic virus almost indistinguishable from that which produces encephalitis.

It may be that the filter-passing organism which produces colds has at times a neurotoxic effect, or it may be that its coming stirs into activity a neurotropic virus that is always present. Certain it is that in some persons a very slight cold or sinusitis will have a markedly incapacitating effect on the brain. I have been struck also by the fact that occasionally, following an injury to the head or a flare-up of infection in the inner ear, the patient will die of acute meningitis, and at necropsy it will be evident that the acute

disease was superimposed on a chronic meningitis and encephalitis which had not been recognized during life. I have also seen a few nervous, incapacitated persons who, after having for some time been reviled and sneered at as "neuros," developed masklike faces and eventually died with definite encephalitis. It may well be, therefore, that at some time in the future, the gastroenterologist and the neurologist will be more keenly on the watch for mild infections with neurotropic viruses.

*Mesenteric Lymphadenitis.* There is one place in the abdomen in which infection can often slumber and this is in the lymph nodes of the mesentery. It has been shown by a number of investigators that bacteria are constantly getting through the intestinal wall only to be stopped in the second line of defense in these nodes, and I have seen a number of cases in which I felt fairly sure that the symptoms of indigestion, abdominal pain, weakness, and slight fever were due to some chronic infection which had overwhelmed these nodes and had caused one or two of them to become calcified and visible in the roentgenograms.

*Disturbances in Circulation.* Considering the tremendous importance of the portal circulation, it is unfortunate that so little is known about it either in health or disease. Marked degenerative changes in the mesenteric vessels are often found at necropsy, but as yet I know of no one who has attempted to correlate these changes with the symptoms presented by the patient before death. It might well be that many of the effects of emotion on the digestive tract are produced through changes in the caliber of the gastrointestinal vessels. It is well known that peptic ulcers are highly sensitive to nervous influences and it may be that vasomotor spasm, nervously produced, is, at times, lasting enough to produce first, anemia of the tissues, and then autodigestion. It is known also that some of the peptic ulcers and especially those that appear suddenly in older persons are due to the plugging of small gastric or duodenal arteries; the resulting shut-off in circulation produces an anemic infarct and then an ulcer.

*Diseases of Nerves.* Another possible cause for disturbances of function in the digestive tract is disease of the abdominal nerves and their ganglia. Many writers have described histologic changes in these nerves but much work remains to be done by more careful and more experienced investigators who will first make certain what a normal ganglion should look like.

I have of late seen several patients with constant upper abdominal pain somewhat resembling that of gall bladder disease but too constant and too little influenced, if at all, by the taking of food. In these cases the cause seemed to be an infection of nerve roots with the virus of herpes zoster. In one case the pain continued for months after the healing of the blisters and in another it was present for weeks before they appeared. The physician will suspect that such injury to the nerves is present when he finds that the pain is

constant hour after hour and day after day and that it is without relation to meals. In some cases pain in the upper abdomen is due to arthritis of the lower dorsal spine with involvement of nerves and muscles.

*Pyorrhea.* I have seen a few cases in which I suspected that the cause of epigastric pain and distress was swallowed pus coming from pyorrhea pockets, and in several of these persons the removal of a few teeth worked a cure within a remarkably short time.

*Pseudo-ulcer.* A group of patients who greatly interest me complain of symptoms which are similar to those of ulcer, but usually not quite the same. Commonly the distress is too persistent; that is, it does not come in attacks with intervals of complete relief. Sometimes also the pain will be present in the morning before breakfast or it will not be relieved in a typical way by the taking of food or alkalis. The expert can often tell from the history that the trouble is probably not due to an ulcer and he will be prepared for the negative report of the roentgenologist. That this report is generally correct is indicated by the fact that some of these patients have been operated on and an ulcer has not been found. Many of them have a decidedly hyperacid gastric juice but this cannot be relied on to account for the symptoms because it is found so commonly in persons who have no discomfort or indigestion.

In many cases the disease seems to be related to nervousness, overwork, and unwise living, and it is best treated by ordering a vacation, by interdicting the excessive use of tobacco, and by changing, if possible, the patient's habits of living and eating. Often nerve sedatives will work better than alkalis.

The question, of course, that bothers these patients is: Is an ulcer going to develop some day? My impression is that perhaps in most cases it will not, but as yet I have no statistical data. All I can say is that I know a number of men who have had the symptoms and the hyperacidity for 10 years or more and who as yet show no sign of ulcer.

**Definite Organic Disease.** *Peptic Ulcer.* Every gastroenterologist, of course, must be keenly interested in the problem of peptic ulcer. What is the cause and why are some persons so highly predisposed to the disease that if one lesion is cut out another will take its place? Mann and his coworkers, who have produced ulcers at will by shunting the alkaline juices of the duodenum into the ileum, have shown that the acidity of the stomach has something to do with the problem, but there are many observations which indicate that there are other more important factors. There are countless persons with marked hyperacidity who do not develop ulcers and there are others with low acids who have one ulcer after another. I suspect, therefore, that we physicians have for a long time been barking up the wrong tree. Some parts of the answer to the problem will doubtless be found through further study of gastric acidity, but it is time now that investigators turned to the study of

some of the other possible factors. It seems to me that we should be learning more about the behavior of pepsin, gastric lipase, mucus, and the dilating fluid in health and disease.

In view of the intimate connection between the symptoms of ulcer and the psychic reactions of the patient it is important to learn more about the ways in which emotion can affect the various secretions of the stomach, duodenum, pancreas and liver. The work of Mann, taken together with the many stories that patients tell about the intimate relation between nervous strain and flare-ups of ulcer symptoms, makes me wonder if duodenal ulcers might not be produced sometimes by a temporary psychic shut-off in the alkaline secretion of the pancreas. It is conceivable also that a nervous spasm of the gastric and duodenal bloodvessels comparable to that which is seen in the hands and feet in Raynaud's disease might keep the gastric or duodenal mucosa anemic long enough so that autodigestion could take place and ulcers could form.

Unfortunately, any really adequate and satisfactory theory of ulcer causation must account for a host of facts and must explain not only the formation of duodenal ulcer but also of gastric and gastrojejunal ulcers. Perhaps, there are different types of ulcers at different ages and in different situations, and we may have to study the causes of all these types. Any adequate explanation of ulcer formation must throw light also on the mode of production of hunger pain. Although much valuable work has been done on the subject, no one of the theories in regard to the causation of ulcer pain satisfies me. It has not yet been explained why the attacks of pain come and go so suddenly, and why alkalies will often give relief when operation or necropsy shows that there has been no break in the continuity of the mucous membrane and no ulcer into which the acid gastric juice could eat.

*Abdominal Pain and Its Relief.* Gastroenterologists still need to know a great deal more about the points of origin and modes of conduction of abdominal pain. It is curious that in a patient under local anesthesia the surgeon can cut the stomach and bowel and can burn holes in it with the cautery without causing distress, but let him just pull on the mesentery or place a clamp on a bloodvessel or even wash off the peritoneal surface of the stomach with warm physiologic salt solution and the patient may nearly jump off the table. Even the injection of a little air into the peritoneal cavity will produce almost unbearable pain in the upper part of the abdomen.

Students of the subject now agree that most, if not all, of the nerve fibers that carry pain sense leave the abdomen by way of the splanchnic nerves. These nerves can be blocked by the injection of drugs from the back, and I believe that the time is coming when more frequently we physicians will be calling in experts in local anesthesia and neurosurgery to help us in giving relief to some of the patients who complain bitterly of pain about the stomach, gall bladder, or colon. We can perhaps learn to make life bearable for

persons who have not received relief from cholecystectomy or gastroenterostomy or appendectomy. It may be that in a given case the anesthetist will first see if the pain can be blocked by injection of one or more nerve roots or rami communicantes. Once the exact point at which blockage can be obtained is known, alcohol may be injected or the nerve may be cut. In a few of the most severe cases the spinal cord may be exposed and small nicks may be made on either side to destroy the tracts which carry sensations of pain. Much work along this line is being done and I hope that something helpful will come out of it.

**Summary.** This paper cannot easily be summarized: about all one can do is to add an index. The subjects treated are: the mechanism of aboral peristalsis; gradients; the nerves of the digestive tract; the mode of production of symptoms of indigestion; gastric secretion; flatulence; disturbances of digestion due to emotion, to constipation, to coarse diet, to constitutional inadequacy, and to migraine; the causes of constipation and diarrhea.

Particular attention has been given to those so-called functional troubles that may really have an organic basis. They might be due to gastritis, enteritis, hepatitis, cirrhosis of the liver, pancreatitis, mild infection with neurotropic viruses, mesenteric lymphadenitis, disturbances in the circulation of the stomach and bowel, or diseases of the nerves in the abdomen.

Suggestions are given as to the possible cause of peptic ulcer and pseudo-ulcer and as to the ways in which abdominal pain may some day be relieved.

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## CLINICAL OBSERVATIONS OF THE IMMUNIZING VALUE OF "NATURAL BACTERIAL ANTIGENS."

### STUDY NO. I.—PNEUMOCOCCI.

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THE specific therapy of pneumonia, as in other acute infections, has taken two courses, namely: (1) The production of passive immunity by the introduction of immune serum; (2) the production of active immunity by the introduction of specific antigens.

1. *Passive Immunity*. Because of the established value of specific antisera in such diseases as diphtheria and tetanus, the greater amount of work has been done in the production and study of such an immune serum for pneumonia. This line of research was greatly accelerated by the report of Cole<sup>1</sup> and his coworkers (1915) of an improved serum for Type I pneumococcus. More recently a serum prepared by the methods of Felton has been intensively studied by Park,<sup>2</sup> Cecil,<sup>3</sup> Bullowa,<sup>4</sup> Rosenblüth.<sup>5</sup> This serum, while polyvalent for Types I, II and III pneumococci, is most effective in Type I infection.

Cecil<sup>3</sup> believes that the maximum reduction of deaths in Types I and II infection has been reached "because this serum is practically 100 per cent effective in the treatment of experimental pneumonia in monkeys. However, in humans we have added the fact that mostly middle-aged and elderly people are attacked, that many of these are alcoholic or have some other systemic disease." 2. *Active immunity* has been produced in animals by Cecil<sup>6</sup> and Zinsser.<sup>7</sup> The production of specific antiserum is the result of active immunity produced in the horse.

Lister,<sup>8</sup> working among the miners of the Transvaal, found that the incidence of pneumonia could be greatly lowered by the use of an immunizing vaccine, not a single case of pneumonia occurring in a period of 9 months in 10,000 recruits. Cecil<sup>9</sup> and his coworkers found that the immunization of troops at Camp Upton, in 1918, reduced the incidence of pneumonia from 30 to 2 per 1000. Lister<sup>8</sup> and Lambert<sup>10</sup> reported a marked reduction in the death rate in cases of pneumonia treated with pneumococcus vaccine.

One of us (Sutton<sup>11</sup>) studied a commercial mixed vaccine similar to that studied by Lambert. Later this vaccine was simplified so that it contained only pneumococci and streptococci. These vaccines were prepared by sterilization with concentrated tricresol, which in the final suspension was diluted to from 2 to 4 per cent.

When this vaccine was discontinued, in 1928, another commercial vaccine was selected because it is sterilized with heat. The results with this latter vaccine were extremely disappointing, the death rate in the treated cases being much higher than in the controls.

During the period before 1930 various methods of preparation of bacterial antigens were studied. These studies brought out the importance of using only the bacterial cell washed free of its medium and excreta; further, that the ideal antigen is as near as possible to the living cell.

Quastel<sup>12</sup> introduced the term "resting" bacteria to designate organisms that are fully mature and endowed with their full potentiality for metabolism, but constrained from multiplication by the withholding of substrates essential for their continued growth. Kendall,<sup>13</sup> studying "resting" bacteria, states: "Bacteria in the 'resting' state are harvested at the height of their growth and

activity, from suitable culture media, washed free from all traces of cultural medium by repeated suspension in physiologic solution of sodium chlorid and centrifugation, and, finally, vigorously aerated to eliminate autoöxydizable substances." "Resting" bacteria initiate chemical changes in substrates which they, as proliferating bacteria, subsequently use for their energy requirements. Prepared in the manner described, they do not multiply unless a suitable source of nitrogen is available.

Resting bacteria are possessed of all the antigenic properties of actively proliferating bacteria, but if used as antigens animal tissues would furnish the nitrogen necessary for multiplication. The addition of a substance that will prevent growth of the bacteria in the presence of nitrogen is then necessary before they may be used as clinical antigens. The substance used should, ideally, prevent proliferation without change in the constitution of the bacterial cell.

Such a preparation of bacteria is the nearest safe approach to a perfect bacterial antigen. This we have called "natural bacterial antigen." Studies of such "natural bacterial antigens" clinically and with laboratory animals have shown that such antigens are remarkably free from reaction, either local or general. For the sake of brevity the term "antigen" will be used hereafter synonymously with natural bacterial antigen. The methods of production of "natural bacterial antigen" will be discussed in a later paper.

Similar preparations of *Streptococcus hemolyticus*, nonhemolyticus, *viridans* and *staphylococci* have been prepared for use as antigens in other infections, and have been found to be free from reaction, either local or general. Powell and Jamieson<sup>14</sup> "found that antigens prepared in a manner used in the preparation of 'natural bacterial antigen' contain intact the more labile antigenic fractions, such as the flagellar antigen. Such antigens produce more potent antibodies in treated animals than those prepared by heat or phenoloid preservatives. This was shown readily with saline suspensions of such bacteria as typhoid, pertussis and meningococcus."

From these experiments they conclude: "Such antigens constitute the closest artificial approach to living bacterial antigens as found in the tissues of the host in natural diseases. This is concluded from experience in using such antigens in the immunization of animals for the production of antiserum."

The question with regard to the treatment of pneumonia by active immunization is not whether an active immunity can be produced, but whether immunity can be produced rapidly enough during the course of the disease to be effective before death occurs. Zinsser found that by the fifth day sufficient antibodies may be produced in rabbits to protect them from lethal doses of pneumococci. From this work he concludes that, inasmuch as in human beings death usually occurs after 6 or 7 days, vaccine, even in severe

pneumonia, might produce immunity early enough to throw the balance in favor of the patient.

Kline and Winternitz,<sup>17</sup> by injections, showed that a large part of the capillary bed is closed by fibrin in pneumonic lungs, and conclude that this may be responsible for the restricted action of serum in this disease.

Our experiments have been carried out in Ward 64 (an adult male ward) of Cook County Hospital. All medical cases, irrespective of diagnosis, are assigned to a medical service, in rotation, by the general admitting service. There are two medical services in Ward 64—Drs. Sutton and Keeton, and Drs. Loeb and Traec. All cases are in the same unit and receive the same treatment, with the exception that those on the Sutton-Keeton service receive in addition the "antigen." This is immediately administered in doses of 1 to 1.5 cc. every 6 hours until the temperature is normal, and then every 12 hours, for 48 hours. Injection is made at four different points, usually in the arm and legs, with the idea that small doses are more rapidly assimilated and that a greater number of lymph glands receive the antigen. The injections are made barely under the skin.

The final development of the "antigen," the results of the use of which we report in this paper, was due to the results previously obtained with commercial vaccines, which are tabulated in Table 1 in conjunction with a summary of the results of Lambert. In these figures and all others given in this paper those cases dying within 24 hours of admission to the hospital have been eliminated; otherwise no selection has been made except as stated below:

TABLE 1.—TOTAL COMMERCIAL VACCINES, WARD 64, COOK COUNTY HOSPITAL, CHICAGO, 1926-1927, 1927-1928: COMBINED WITH LAMBERT'S RESULTS AT BELLEVUE HOSPITAL, NEW YORK.

	Treated with vaccines.			Controls.		
	Total cases.	Died.	Mortality, per cent.	Total cases.	Died.	Mortality, per cent.
Cook County cases	262	80	30.1	299	128	42.8
Lambert's cases	221	47	21.2	286	116	40.5
Total cases	483	127	26.3	585	244	41.7

In the total series 483 patients (Table 1) were treated with commercial vaccine, with 127 deaths, a mortality of 26.3 per cent. As controls, 625 cases were used, with 259 deaths, or 41.7 per cent—a reduction of deaths following the use of vaccines of 15.4 per cent, or a reduction of 37.1 per cent in mortality.

The work with the "natural bacterial antigen" began in January, 1930. During 1930 the pneumonia incidence was low, and as the study was under the control of a resident (Dr. Rosenblum), some cases in other wards were treated. During January of this year (1931) the cases are from Ward 64 only. As the number of control



cases for this period is relatively small (41), the average of all controls is also used in Table 2. As a further control, all the adult cases of lobar pneumonia (no children are included in any of this study) occurring in the hospital during the years 1927, 1928 and 1930, exclusive of 24-hour deaths and those previously used as treated cases or controls, were tabulated. The year 1929 is not included because no cases were treated with "antigen" during that year, this being the period during which various methods of preparation were studied. During this period of 1927, 1928 and 1930 there were 2679 cases of lobar pneumonia, with 894 deaths, or 33.3 per cent.

TABLE 2.—RESULTS OF TREATMENT OF PNEUMONIA WITH "NATURAL BACTERIAL ANTIGEN" COMPARED WITH CONSECUTIVE CONTROLS, AVERAGE OF CONTROLS OVER FOUR YEARS, AND WITH 2679 CONSECUTIVE CASES OF LOBAR PNEUMONIA, EXCLUSIVE OF CASES PREVIOUSLY COUNTED AS TREATED OR CONTROLS. (Those cases dying within 24 hours of entrance to hospital have been omitted.)

Treated with bacterial antigen.			Control cases.		
Total cases.	Died.	Mortality, per cent.	Total cases, Ward 64.	Died.	Mortality, per cent.
129	29	22.5	339	143	42.1
		Cases of lobar pneumonia	2679	894	33.3
		Ward 64, 1930 . . . .	41	17	42.5

It will be noted that the term "lobar pneumonia" has been used only in this last group of cases which are used as controls. However, in the other group all cases, both treated and controls, included lobar pneumonia, bronchopneumonia and various so-called terminal pneumonias. Thus it will be seen that the "antigen" treated cases gave favorable results, even when compared with a large number of lobar pneumonias.

Of the 129 cases treated with the "antigen" 29 died, a mortality of 22.5 per cent. Compared with all controls (339 control cases in Ward 64, 1926 to date—except 1929—with 42.1 per cent mortality) this shows a decrease of 19.6 per cent, or a percentage reduction of 46.5 per cent. If these antigen-treated cases are compared with a large series of straight lobar pneumonia (33.3 per cent mortality) there is a decrease of 10.8 per cent, or a reduction of 32.7 per cent.

It is believed that these results offer strong evidence that bacterial antigens are of value in the treatment of all types of pneumonia. Further, in view of the poor results obtained by Sutton with a heat-killed vaccine, the better results obtained with a commercial vaccine, and the still better results with a method of preparation which changes the bacterial protein the least, we are led to believe that the variable results from different antigens depend largely upon the method of preparation. If this be true it then becomes necessary to restudy the entire field of vaccine therapy.

Conclusions. 1. An improved method is suggested for the preparation of bacterial antigens.

2. Bacterial antigens prepared in this manner are nontoxic.
3. Bacterial antigens may be given early in the disease, without awaiting the typing of the pneumococcus.
4. The results with "natural bacterial antigen" are not spectacular, but they compare favorably with the results reported with the use of antipneumococcic serum.
5. As the results with "natural bacterial antigen" are on even terms with the specific sera, it should be used until its value is determined.

NOTE.—The antigen used during 1930 was made according to our methods under the personal supervision of Mr. Jamieson and Mr. Powell of the Biologic Research Division of Eli Lilly & Sons Company.

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### THE DIAGNOSTIC PROGRAM IN FOOD ALLERGY.\*

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For the purposes of this discussion we shall adopt a broad interpretation of the term food allergy as brought out in the following illustration. If, following a banquet, most of the participants

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become ill, something was wrong with the food. If, on the other hand, with all eating the same food only one individual becomes ill, something was probably wrong with that individual. The first was an instance of food poisoning, the second of food allergy.

**Symptoms Referable to the Enteric Tract.** *Grande Anaphylaxie.* The "grande anaphylaxie" of the French, or acute anaphylactic shock, is the most startling and tempestuous of the responses to allergenic ingestants. Fortunately it is exceedingly rare. It consists in a severe acute reaction with nausea, vomiting, diarrhea, sometimes bloody, violent pain, often urticaria, circulatory collapse and even death within minutes or hours after eating the allergenic food.

*Acute Food Allergy.* Probably the two most nearly pure allergic responses are the gastric response, with nausea and vomiting and sometimes diarrhea promptly after eating the allergenic food, and the colonic response, with allergic colitis usually of the mucous colitis type. Often allergic digestive disturbances are accompanied by attacks of urticaria or angioneurotic edema, and one frequently obtains the history of other allergic manifestations either in the patient himself or in his family. But neither of these need necessarily be present.

*Subacute and Chronic Gastrointestinal Allergy.* Subacute or chronic abdominal allergy may manifest itself as a hyperperistalsis, especially in the colon, and with an increased secretion of mucus, in which eosinophils and Charcot-Leyden crystals may be found. Diarrhea is not a necessary accompaniment. Just as nervous indigestion may produce either diarrhea or constipation, food allergy may manifest itself with either of these responses. In either case we are dealing with smooth muscle spasm.

Cyclic vomiting is, in my experience, not infrequently a manifestation of food allergy. I have under observation just now 3 children with cyclic vomiting, 1 of whom has an associated allergic headache, while the other 2 have associated asthma. Balyeat<sup>1</sup> has recently presented evidence that the child with cyclic vomiting is likely to become the adult with migraine.

When we consider the type of pathologic response with muscle spasm, serous exudation, edema or internal hives, hyperemia and increased catarrhal secretion of the lining mucosa; and when we realize that the shock tissue may lie anywhere from the mouth to the anus and that in one individual different levels may be responsive at different times, we can more readily understand the frequent indefiniteness and variation in symptomatology in the individual case.

*Allergy Complicating Organic Gastrointestinal Disease.* While in my experience colonic symptoms most frequently accompany abdominal allergy the symptoms may closely imitate those of ulcer, appendicitis or of bile-tract disease. Indeed, food allergy may actually accompany a true organic state, thereby complicating the picture and the treatment.

A person with true cholecystitis will often remark that he cannot eat certain specific foods without exacerbation of symptoms. Here I believe we are often dealing with an associated food allergy in which ingestion of the specific allergen produces a local allergic response in the bile tract with resultant exacerbation of the cholecystitis. Vally Menkin<sup>2</sup> has demonstrated that foreign protein introduced into the circulating blood accumulates in an inflamed area, where it is found in greater concentration than in the normal tissues. He thus confirms the earlier work along the same line reported by Auer.<sup>3</sup>

**Methods of Study and Treatment.** I would divide the history of dietary treatment based on allergy into three epochs. The first, before the days of clinical allergy and skin testing, is represented by the empirical diet lists with which we have all been familiar in the past. To a certain extent they were based on experiences with cases of food idiosyncrasy, and included for a given symptom complex those foods which had been found by experience to be least productive of symptoms in the largest majority of individuals. Such were the diets for gall-bladder disease, mucous colitis, and the more obscure forms of chronic indigestion.

The second epoch was ushered in with the development of the sensitization test, when it seemed probable that by the simple process of applying solutions of the food allergens to the abraded skin, one could determine definitely to what food a patient might be intolerant. This was a decided improvement, and those who have used the method have clearly established that many allergenic foods can thus be discovered. At the beginning it appeared to be a splendid stereotyped method for determining the appropriate diet in the individual case. But as time went on even the enthusiast in skin testing was forced to the conclusion that some foods which definitely disagreed would not infrequently fail to give positive cutaneous reactions and that some that gave positive reactions would not be productive of symptoms.

So, in the third epoch in which we now find ourselves, we observe a combination of the methods of the first two with, in addition, a more rational and scientific systematization.

The allergic concept has taken food idiosyncrasy out of the limbo of curiosities and has placed it in the group of diseases of known etiology. The sensitization reaction has explained food idiosyncrasy and has enabled us to recognize hitherto unrecognized offending foods. This is especially true of the foods which are eaten daily and which therefore remain otherwise unsuspected. Realization of the deficiencies of the skin-test method have led to the third epoch, represented by the diagnostic use of the food diary and the trial diet.

*The History.* The anamnesis is as important in the case of allergy as in a neuropsychiatric case. From the past history and

the family history one will determine the probability of an allergic state, bearing in mind, of course, that such may exist in spite of an otherwise entirely negative personal and family history. The patient will sometimes suspect certain foods, and at times a careful discussion of each attack will suggest previously unsuspected foods. A history of seasonal variation will occasionally furnish good clues.

*Physical and Laboratory Examination.* It is only necessary to state here that the allergist who fails to make a thorough study of his cases from all angles, including roentgen-ray examination when necessary, will often fail to recognize other associated organic diseases in the gastrointestinal tract and elsewhere and will, as a consequence, fail in his treatment, in a measure proportionate to the importance of the associated disease.

*Skin Testing.* Regarding methods of skin testing I shall only say that both the scratch method and the endermic or intradermal technic have a distinct place. The latter is much the more sensitive but for safety's sake should not be done without preliminary scratch studies.

Assuming that with the sensitization studies we have identified certain allergenic foods in a case of presumptive abdominal allergy, the first step in treatment will be the elimination of the offending foods from the dietary. This may be all that is necessary, but sometimes other factors must be considered in the diet. In allergic mucous colitis, first described by the writer in 1922, I have emphasized<sup>4</sup> that by the time the case presents himself for treatment there are usually several factors other than the allergy which require treatment. The mechanical irritation of chronic constipation or from roughage diet, the hyperemia of a chronic diarrhea, repeated insults from chronic catharsis, possibly also secondary infection, all require attention.

*Food Diary.* If the skin tests are negative or if, after trial, we conclude that all of the allergenic foods have not been discovered, two other methods of study remain. These are the food diary and the trial diet. These have distinct spheres of usefulness. If the symptoms are practically continuous and presumably the offending food is being eaten daily or nearly so, the food diary is not likely to solve the problem. Instead, the patient is placed on a trial diet from which those foods which experience has shown to be frequently allergenic have been eliminated. If, on the other hand, symptoms manifest themselves at intervals of several days, the food diary is employed. (Chart I.) The patient tabulates all substances which pass the lips. Each day he adds any new food at the bottom of the list. In the column for each day he checks all foods eaten on that day. Methods of cooking and food combinations show on the table. It is not sufficient for example to record "eggs." Scrambled eggs and omelets are reported as two entirely different foods. Roast beef and beefsteak are separated. Salads are classified according to all of their constituents.



Days on which symptoms are manifest are checked. Not infrequently certain foods stand out as being frequently or constantly present on those days or on the preceding day. Sometimes combinations of two foods are suspected. These are then avoided for a period sufficiently long to determine whether they were actually allergenic. At the same time the diary is continued in further search for offending foods.

A record of the foods eaten is not sufficient. On the reverse of the chart the patient keeps a diary of the events of each day. I am indebted to Dr. Alvarez for a most striking example of the value of a record of the events of each day. The case was that of a man in whom food allergy was suspected but in which the usual methods of study had failed to demonstrate the cause. The patient was a railroad man and his run would carry him at intervals to a certain large city. It developed from the study that his attacks would invariably occur either on the day of his visit to the city or on the following day; the attacks had some relationship to his visiting the city. Now he was very fond of cheese and there was a certain restaurant in this city where he could procure a certain brand of cheese which was especially to his liking. This, it developed, was the offending allergen. In such a case the food diary would have failed because cheese was eaten both in the city and elsewhere. The observation that attacks followed trips to the city led ultimately to the discovery that cheese eaten at home was innocuous and that only the special brand mentioned caused trouble.

*Trial Diet.* We are indebted especially to A. Rowe<sup>5</sup> for the clinical use of the elimination diet, a method which has not yet become popularized but which I have found indispensable in my study of food allergy. Rowe tabulated the frequency of sensitiveness to the different foods in a large number of allergic cases and selected from this table those foods which from experience had been found to be the most infrequently allergenic. These he built up into a series of 5 elimination diets. If after 2 weeks or more on one such diet the patient is not relieved, another is substituted which contains few or none of the foods listed in the first diet but which is still made up of infrequently allergenic foods. He often finds that on one or another of these elimination diets the patient became symptom-free. This is then used as a basic diet and single foods are slowly added to it over a period of weeks. Any new food which is found to produce symptoms is permanently excluded. In this way all of the offending foods may be gradually discovered.

*Biologic Food Groups.* Until very recently no attempt had been made to classify the vegetable foods biologically as has been so well done with the pollen allergens. The writer has presented such a classification, and his study of food allergens in relation to this grouping has led to some rather interesting observations<sup>6</sup> (Table 1). Those that bear on the subject in hand may be briefly summarized

as follows: Where one member of a biologic food group has been proven to be allergenic to an individual, other members of the same group may cause allergic symptoms, even though their skin-test reaction has been negative. Sometimes a positively reacting member of a group is found to give rise to no symptoms whatsoever, while a negatively reacting member of the same group does cause trouble. If one is sensitive to one member of a group it does not necessarily follow that all other members will produce symptoms. It only indicates the need for caution in the eating of the other members until it has been definitely determined whether they are allergenic or not.

TABLE 1.—THE BIOLOGIC GROUPING OF THE COMMONER VEGETABLE FOODS.

<i>Graminae</i>	<i>Chenopodiaceae</i>	<i>Pomaceae</i>	<i>Umbelliferae</i>
Wheat	Spinach	Apple	Carrot
Rye	Beet	Pear	Parsnip
Barley	Swiss chard		Parsley
Oat		<i>Drupaceae</i>	Celery
Rice	<i>Cruciferae</i>	Almond	
Corn	Radish	Plum, prune	<i>Solanaceae</i>
	Turnip	Cherry	Potato
<i>Liliaceae</i>	Rutabaga	Apricot	Egg plant
Onion	Mustard	Peach	Tomato
Garlic	Cabbage		
Asparagus	Kale	<i>Leguminosae</i>	<i>Cucurbitaceae</i>
	Brussels sprouts	Peas	Pumpkin
<i>Polygonaceae</i>	Kohlrabi	Beans	The squashes
Buckwheat	Cauliflower	Lentil	The melons
Rhubarb	Broccoli	Peanut	Cucumber (pickles)
<i>Juglandaceae</i>	<i>Rosaceae</i>	<i>Rutaceae</i>	<i>Compositae</i>
Black walnut	Blackberry	Lemon	Salsify (oyster plant)
English walnut	Raspberry	Orange	Chickory
Pecan	Strawberry	Grapefruit	Endive
Hickory			

NOTE.—Vegetable foods not listed are not closely related to other foods.

These observations have a definite application in the formulation of the elimination or trial diet. In the dietaries formulated by Rowe and others different foods appear in the five different diets, but they are sometimes very closely related biologically.

My own trial diet is therefore based not only upon knowledge of what foods rarely give positive skin reactions, but also upon an understanding of the biologic grouping of foods. The occurrence of crossed reaction within biologic groups appears not to be extremely frequent, and diets such as Rowe's will usually suffice, but in the event relief from symptoms is not obtained with them, one should bear in mind that crossed reaction may be responsible for failure, and should take steps to eliminate entire biologic groups rather than individual foods.

In the formulation of my trial diet I have made a study of the frequency of the positive food reactions as I have observed them in the southeastern States and compared it with Rowe's study for the Pacific coast.<sup>7</sup>



From a comparison of these 2 tables I have arranged a base list or foundation list of foods consisting of, first, those foods which are infrequently allergenic and second, foods such as are not closely related genetically to others. (Table 2.) The patient is first tested with the food allergens. Those foods to which he gives positive reactions as well as foods belonging in the same biologic group are then eliminated. This, of course, applies also to the foundation list. Foods which the patient from his own experience has suspected of causing trouble are also customarily eliminated. The remaining, apparently innocuous foods, now form a list from which articles may be selected to be built upon the foundation list, to provide a fairly well-balanced diet. Since the trial diet is rarely used unaltered more than 2 weeks, it need not be perfectly balanced as regards food value. Only one meat and one cereal are added at the beginning, preferably such as are not eaten routinely. The choice is usually between rye, corn and rice among the cereals and lamb and fowl among the meats. Additions are made gradually with the vegetables and, as a rule, all the members of one biologic group are added before proceeding to a new group. If one member of a food group produces symptoms it does not necessarily follow that other members will do likewise, but special watch is made of the effects of other members of the group. As a rule, new foods are added singly and not oftener than one every third day.

TABLE 2.—BASE LIST OF FOODS FOR USE IN THE FORMULATION OF THE TRIAL DIET.

Pineapple	Huckleberry
Mulberry	Cranberry
Fig	Olive
Buckwheat	Sweet potato
Rhubarb	Salsify (oyster plant)
Hazelnut, filbert	Chicory
Chestnut	Endive
Currant	Artichoke
Gooseberry	Sugar
Pistachio nut	Salt
Okra, gumbo	Maple syrup
Tea	Gelatin

It is obvious that Rowe's 5 trial diets may be employed without previous skin testing. If one has gone through all 5 diets and the patient is not relieved, and if we are still reasonably sure that we are dealing with food allergy one should then have recourse to the sensitization test to see if it will shed further light. With the trial diet which I have described, the sensitization test should be done first since the selection of foods for addition to the foundation list will depend in great measure upon the positive reactions observed and their relationship to other members of the food groups.

**Discussion.** From the preceding it develops that in a case of suspected food allergy the diagnostic survey has really only commenced at the completion of the sensitization studies. Although

food tests as performed today are not over 50 per cent accurate diagnostically, they make the best point of departure at the beginning of the study, for when positive they provide a definite starting point in the formulation of the diet. If their use decreases the amount of subsequent necessary investigation by 50 per cent or even by but 25 per cent, they are well worth employing. With the completion of these tests the results are correlated with the patient's dietary history and a tentative diet is arranged. Any allergic diet must be followed rigorously for at least two weeks before we can be certain of results. If, after this, symptoms persist, we may have recourse to the food diary, where symptoms are intermittent or the trial or elimination diet where they are more constant, or indeed, a combination of both. For example, after a patient has been placed on the trial diet we will often have him keep a food diary at the same time. The limitation of his diet facilitates the study of the food diary.

Finally, I would emphasize that it is not sacrilege for the allergist to employ other therapeutic measures than purely allergic, directed against the other related nonspecific factors such as intestinal stasis, bile tract infection, ulcer, diabetes, tuberculosis, etc. In the treatment of gastrointestinal allergy the gastroenterologist and the allergist stand on common ground and each should avail himself of the therapeutic advantages made possible by the other.

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#### SYDENHAM'S CHOREA.

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CHOREA is a general term covering a number of disease entities. This paper will deal only with Sydenham's chorea, a disease which was first described by Sydenham in his "Schedula Monitoria"

in 1686 and later in his "Processus Integri" in 1693. Both of these works gave a very brief but accurate account of the disease as it is now described. With your permission I shall quote from the "Processus," Chapter XVI, on "St. Vitus' Dance:": "This is a kind of a convulsion which attacks boys and girls from the tenth year to the time of puberty. It first shows itself by limping or unsteadiness in one of the legs which the patient drags. The hand cannot be steady for a moment; it passes from one position to another by a convulsive movement however much the patient may strive to the contrary. Before he can raise a cup to his lips he makes as many gesticulations as a mountebank, since he does not move it in a straight line, but has his hand drawn aside by spasms until by some good fortune he brings it at last to his mouth. He then gulps it up at once so quickly and so greedily as to look as if he were trying to amuse the lookers-on."

The treatment used by Sydenham might also be of interest. The patient was bled one day some 8 ounces, the next day he was given a concoction of black cherry water, aqua epileptica Langii, venus treacle, and liquid laudanum. The bleeding and catharsis were alternated daily for several days, or as long as the patient's physical condition showed that he was able to stand the treatment. On the days when there was no purging the patient was given a very complex shotgun prescription. Plasters were oftentimes applied to the sole of the foot to guard against relapse. It was also advised that the patient be bled and purged for a few days each year at about the time of the expected onset of the condition. It is interesting to note that Sydenham also suggested that the above treatment might be of value in epilepsy of adults, but added that he had not given it a trial. Since the time of Sydenham many different types of treatment have been suggested for chorea, however, the treatment used at the present time is but slightly more specific than that suggested by Sydenham.

The disease is also spoken of as St. Vitus' Dance. Toward the end of the 14th century a curious mania developed in Germany, the individual so affected performing a wild dance which had the appearance of a person "possessed of the Devil." St. Vitus at that time had considerable fame as a protector against all kinds of sickness but particularly those supposedly due to afflictions by the Devil. Since the movements of Sydenham's chorea resembled to some extent the movements of these people, it came to be called St. Vitus' Dance.

**Etiology.** At the present time there is no commonly accepted specific etiology for Sydenham's chorea. It is generally supposed that infection of some sort may be a precipitating factor. There seems to be without much doubt a predisposition on the part of the patient to the development of the disease. This predisposition, or hereditary factor, may be dependent upon an inferior integration

of the psychomotor cerebellar mechanism. This is often seen in children who never develop chorea; we say that the child is in the so-called awkward age. In children who have such a predisposition toward the development of chorea we need only to postulate a minor infection to disturb the normal integration of motor characteristics.

The infections which are particularly prone to precipitate the development of chorea are usually of the streptococcal type, such as scarlet fever, acute streptococcal tonsillitis, and acute rheumatic infections. In addition, many of the other children's diseases may serve as the secondary causative agent. It is remarkable how many of the children in this series had a history of whooping cough, measles and chickenpox, while diphtheria and scarlet fever occurred only occasionally. Pneumonia was recorded in a number of instances. It seems of particular interest to note that in the whole series there are recorded only five cases of tonsillitis, and in 2 of these the tonsils had been removed before the onset of chorea. The importance of tonsillitis as a factor in chorea has also been minimized by a number of other authors. Comparatively few cases had a history of acute rheumatic fever, yet a relatively large percentage of these showed physical signs of endocarditis.

The "theory of infection" as a cause for chorea is not new. Todd, in 1840, believed chorea to be rheumatic in origin. Wilson, in 1843, attributed chorea, not to the nervous system, but to "morbid blood" affecting the muscular system. Kirkes, 1863, and Hughlings Jackson, 1869, believed chorea due to showers of minute emboli projected into the cerebral vessels causing minute thrombi. Jackson located the seat of the lesion in the nerve tissues near the corpus striatum. Broadbent, in 1869, stated that he felt chorea was a symptom rather than a disease and could not be referred to any single pathologic lesion. In 1889 Maragliano believed that chorea was the result of a toxic infectious process, thus originating the so-called toxic infectious theory of the disease.

The relation of rheumatic fever to chorea has been variously estimated. Some feel that it is the chief exciting cause of chorea, while others consider that there is little more than a coincidental relationship between them. In this series it is interesting to note that rheumatic fever was noted either during the course of the disease or before the onset of the movements in about 33 per cent of the cases, while in an additional 15 per cent some evidence of cardiac disturbance was noted. This makes a total of approximately 50 per cent in which there was evidence of rheumatic fever or cardiac involvement. However, in a number of these cases an acute infection preceded the development of symptoms whether these symptoms were of acute rheumatic fever or chorea. The most common infection seems to have been either scarlet fever or measles, or both.

All cases but one presented either a history or physical evidence

of some infectious disease or of acute infection which preceded by a short period the onset of symptoms of chorea. The one exception had an impacted tooth, the removal of which was followed by a rapid disappearance of choreiform movements. Those cases showing evidence of rheumatic fever are included as cases of infectious disease. Various other causative factors have been suggested; *e.g.*, a number of authors have remarked upon the importance of oral infection as a precipitating factor, perhaps even as the cause of choreic movements, and they cite cases in which such infection has been removed and has resulted in an almost immediate cure. Impacted teeth have likewise been blamed, the removal of which results in miraculously quick cures. In 1928 an author claimed to have cured a case of sciatica by injection of the nasal ganglion with alcohol, and by the same means he secured an equally remarkable cure of chorea. We find cases reported in which choreic movements have subsided immediately after the patient had been given a vermifuge.

Too little significance has been attached to the psychic factor in the production of chorea. Many cases, perhaps those predisposed, seem to be precipitated into an acute attack by a fright or other violent emotional upset. In these cases a complete examination oftentimes reveals no evidence of an organic factor which might account for the symptoms.

**Age and Sex Incidence.** Chorea is most commonly seen, as was originally described by Sydenham, between the ages of 10 and 15 years. It may occur as early as 5 years and as late as 20 or more. It is essentially, however, a disease of childhood. Females seem more prone to the disease than males. In the literature the ratio is given as 3 to 1, or 2 to 1. In this series of 125 patients, although not sufficiently large for statistical value, the ratio is about 2 females to 1 male. As to race incidence there seemed to be little or no choice, the American or mixed stock showing the highest percentage, the Irish being second with about 23 per cent, Hebrews with approximately 21 per cent, while Hungarian and Italian children each constituted about 8 per cent of the group studied. There was one pure negro child with the disease. This is interesting because a fairly large percentage of the patients coming to the clinic during the period this work was being carried on were negroes, and so the finding of only one colored child with chorea is perhaps rather surprising. It is perhaps worth while to note that there is a seasonal variation in the disease, its first occurrence being in the spring or fall. Recurrences likewise usually appear at these same periods of the year.

**Symptomatology.** Sydenham's chorea is characterized by irregular, involuntary, jerky, spasmodic movements which are fairly rapid and of a comparatively wide range. The degree of involvement is extremely variable, being from only one or two muscle

groups to practically the entire body. In some cases there may be noted only twitching, purposeless, jerklike movements of the face, usually on one side, or there may be similar movements involving a finger, hand, all of one extremity, or perhaps half of the body, while in some cases the whole body may be involved in this hyperkinesis. Most patients have involvement of one side first and in many cases the disease remains unilateral. Bilateral involvement, however, is not uncommon. When this occurs the arms and legs are seemingly poorly controlled and are swung about in a wobbly, awkward fashion. In severe cases walking is usually absolutely impossible. There may be involvement of the respiratory system, making the breath come in gasps and groans; the patient may have difficulty in talking. In the milder cases the movements usually cease during sleep, while in the more severe ones the movements may be continuous. In the paralytic types of chorea there may be hemiparesis with a hemiplegic type of gait, a dragging of the extremity on the affected side and inability to use that extremity. The patient in attempting to drink from a glass may eventually be able to get the fluid to his mouth, but is more likely to drop the container. One often gets a history of the child being punished by his parents for being careless, breaking dishes, and the like.

The patient frequently presents mental symptoms as well as the motor symptoms described above. These may be spoken of as periods of emotional instability, fretfulness, peevishness, and unreasonableness. The little patient is tearful, cries at the slightest provocation, is difficult to manage, and seems almost unable to remember. Frequently his sleep is disturbed by horrifying, unpleasant dreams, the content of which he is rarely able to reproduce. There is often a rather characteristic facial expression, the so-called choreic facies. This is best described as an expression of wistfulness. In some cases the loss of memory may be marked and may be associated with deafness, confusion and disorientation. It is unfortunate that in many of these cases the parents fail to realize the seriousness of the disease with which their child is afflicted and for the many little peculiar mental twists, emotional and physical characteristics the child is scolded or punished. This, of course, simply serves to accentuate the symptoms present. It is unfortunate, indeed, that parents do not realize these facts before they have increased the child's disability by ill-advised scolding and punishment.

On examination one finds a diminution and sometimes an absence of the tendon reflexes. They are quite often variable in the same patient. Signs of pyramidal involvement are not infrequent. In some cases there is a definite tendency toward hypotonicity, particularly on the side most affected. The more important signs, however, are those of incoördination of movement, such as adiadochokinesia and asynergia. Such signs are, of course, more prominent on the affected side and are particularly noticeable in those cases

in which there is hypotonia. The patient is absolutely incapable of synergising the normal motor functions and particularly is he unable to carry out complicated associated movements. The apparent muscle weakness which is so frequently noted does not seem to be a true muscle weakness, but rather the result of the continuous movement, of the hypotonia, and of the incoördination.

Sensory symptoms in chorea are comparatively infrequent. Occasionally, but very rarely, the patient will complain of pain and these cases have been described as "painful chorea." Objective sensory signs have not to my knowledge been described.

Some cases of chorea manifest a fever of varying degree, but in most patients examined at the clinic the acute symptoms of infection have disappeared and the temperature has returned to normal, so that it is rare in the usual run of clinic cases to find a rise in temperature.

**Blood Findings.** The blood chemistry is in most cases essentially normal. The white blood cell count may be moderately increased. The blood Wassermann is not infrequently positive, particularly in chronic cases. Chronic cases seem often to be associated with hereditary syphilis. The spinal fluid may show a pleocytosis of moderate degree.

**Pathologic Anatomy.** The pathology of the average case of chorea minor is not much better known than its etiology, since very few cases ever come to autopsy. Those cases which are fatal are usually so acute and present such an exaggeration of symptoms, that it is doubtful whether we should consider the lesions found in these cases to be those of the usual or average case. It is usually considered, however, to be a type of encephalitis involving both the cortex and basal ganglia, but more particularly the basal ganglia region with the greatest involvement in the corpus striatum. There has been described dilatation of the capillary blood vessels and a type of perivascular infiltration with punctate hemorrhages which eventuate in a type of granular degeneration. In a recently reported case showing choreic symptoms on one side of the body, a postmortem of the brain showed destruction of the corpus Luys with involvement of the descending fibers on the opposite side. This author concludes that the impulses for the movements seen in chorea arise at a lower level than the corpus Luys, and he goes so far as to state that the choreic movements do not appear providing the corpus Luys is intact. In some cases with coincidental endocarditis there has been noted chromatolysis of practically all cells of the central nervous system with swelling and eccentric displacement of the nuclei, also curious fatty deposits in the large cells of the motor cortex and the small cells of the pallidum. Fat has also been demonstrated in the perivascular spaces. In some cases rheumatic nodules have been described in the brain. It is, I believe, fairly safe to consider that the pathology of chorea is that of a generalized

encephalitis which involves, predominantly the basal ganglia, and particularly the striatum. We may theorize somewhat and say that the movements of chorea are the result of the removal of the inhibitory influence of the higher physiologic levels with consequent overfunction of lower motor areas. Obviously, since the destruction is rarely if ever complete, the inhibitory influence is not completely removed and the movements retain some suggestion of normality.

**Treatment.** The multiplicity of treatments suggested for Sydenham's chorea is evidence enough that most of them are unsatisfactory. The first and most important dictum in the successful treatment is rest, absolute rest in bed with isolation of the individual from all possible stimuli, particularly social stimuli. This means mental as well as physical rest and therefore reading, toys, and the like are contraindicated. In addition to the absolute rest, a good nourishing diet with plenty of vegetables but with a low meat ration is essential. The second important dictum in the schedule of treatment is the elimination of foci of infection. Many authors favor the elimination of these foci, such as septic tonsils and septic teeth, immediately upon admission of the patient to the hospital. However, it seems to me that it is better and much more satisfactory to the patient to wait until the movements have either ceased or are much decreased. If at the time of admission there is a fever, the elimination of foci should wait until the temperature has returned to normal. In support of the above I would point out the large amount of work done showing that removal of tonsils, teeth, and other foci has apparently not changed the course of the disease in the slightest. In addition, if the patient at the time of admission is particularly easy to disturb emotionally, early operative procedures may cause a serious psychic shock to the patient.

Sera of various types have been suggested in the treatment of chorea. Some authors advocate a serum made from the patient's own blood and given intraspinally. Others, *e.g.*, Rosenow and Small, have developed sera which are supposed to be specific for the disease. The authors of these various treatments report a remarkably high percentage of cures but unfortunately their results have not been substantiated by other workers in the field. Cases of chorea have been reported as recovering after lumbar puncture, the recovery being explained on the basis of relief of pressure on the brain. There have been reported some cases of chorea treated by epinephrin which showed marked improvement. However, other authors trying to substantiate these results have been unable to report similar findings.

Foerster's theory is that each movement is composed of two constituents, a corticospinal and a corticothalamopallidal component, the latter component being constantly inhibited by the striatum. A lesion of the small cells of the striatum or striopallidal fibers



would then give an unequal inhibition and result in an ataxia of movement. Working on this hypothesis Marinesco, Sager, and Diniochiotu have elaborated a treatment by the use of sodium luminal and magnesium sulphate which is said to give good results, since sodium luminal and magnesium sulphate inhibit the action of the diencephalon and the mesencephalon. The luminal treatment consists in subcutaneous injections twice daily of 0.22 gram of sodium luminal over a period of 20 to 25 days. At the same time the patient is given magnesium sulphate intraspinaly, in a dosage of 8 mg. per kilogram of body weight. These injections are likewise repeated every day for 26 days. I have had no experience with this type of treatment.

Some authors believe that the course of chorea is shortened by the use of arsenic in various forms, the favorite form, of course, being Fowler's solution. Personally, I do not believe that Fowler's solution influences the course of the chorea in any way.

In those cases associated with rheumatic involvement it is usually of value to include salicylates in the treatment.

A treatment which has received a great deal of attention lately is the nirvanol treatment, nirvanol being phenyl-ethyl-hydantoin. A number of authors have reported the use of this drug with very beneficial results. They feel that improvement is more marked in the more severe cases. In some of the milder cases it seems to have little or no influence. The drug is reported as being dangerous in that it may produce a leukopenia with eosinophilia, or even agranulocytosis. It is not to be administered over a period of more than 10 days. The dosage in young children is 5 grains a day; in older children, 10 grains a day, to be given over a period of from 7 to 9 days, or until the development of the so-called nirvanol sickness. On about the seventh day there usually appears a fever which reaches its maximum on the ninth day and subsides on the eleventh day. The drug is discontinued when the fever or a rash appears. Usually on the ninth day a reddish-brown maculopapular eruption appears on the thighs, wrists and abdomen. In 1 or 2 days it becomes a generalized urticaria-like eruption. There may be an associated intense pruritus. The leukopenia and eosinophilia are seen in most cases, agranulocytosis and other ill effects, such as hemorrhagic nephritis, occurring but rarely. No work has been done on the localization of the drug in the central nervous system, but it is supposed to act on the thalamus and corpus striatum. In one series the duration of the disease in the control cases averaged 115 days, while the nirvanol treated cases averaged 31 days.

**Conclusions.** Sydenham's chorea is a disease of childhood, 80 per cent of the cases occurring between the ages of 5 and 15 years. It does, however, occur in younger and in older children. The incidence in females is twice that in males. It is a disease characterized by irregular, involuntary, jerky, spasmodic, moderately

quick movements associated with some depression of the tendon reflexes and possibly evidence of involvement of the pyramidal pathways. The disease is practically always associated with mental symptoms during the acute stage. These mental symptoms are in effect a variance of the normal personality reactions. These variations may be accentuated rather markedly by ill-advised handling and treatment, particularly in the home before the disease is recognized. The disease most likely occurs in individuals in whom there is a predisposition which is the result or cause of a poor integration of the cerebrocerebellar motor mechanism.

Pathologically it is a type of encephalitis characterized by involvement of both the cortex and basal ganglia, but particularly of the corpus striatum and perhaps the corpus Luys.

The most essential part of the treatment of chorea is absolute mental and physical rest, best obtained by the removal of the patient from his home and placing him in an institution where his environment can be properly controlled. The multiplicity of treatments suggested are evidence of their inadequacy. The removal of the foci of infection is important but should be delayed until the child has become accustomed to his new environment, until there has been a diminution in the movements exhibited, and until the fever which the patient may have has disappeared. Infections such as acute rheumatic fever, acute tonsillitis, acute nephritis, and scarlet fever, are coincident or precipitating factors and are not the primary causes of Sydenham's chorea.

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## CREATINURIA IN HYPERTHYROIDISM.\*

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COMPARATIVELY few clinical studies of the disturbances in the creatin-creatinin metabolism in hyperthyroidism are recorded in the literature.

Shaffer (1907) was the first to point out that creatinuria occurred in exophthalmic goiter. He found creatin in the urine in 8 of 12 cases studied. In some cases the creatin excreted exceeded the creatinin excreted. The latter was found always to be very low in

\* Abstract of thesis submitted by Dr. Kepler to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine, 1929. Submitted for publication January 21, 1931.

amount when the creatinin coefficients were calculated. Denis and Minot (1917), and Denis and Kramer (1917) presented data suggesting that the amount of creatin excreted in cases of exophthalmic goiter was dependent on the intake of protein, and that it was increased by a diet high in protein and decreased or even abolished by a diet low in protein. Denis and Minot (1919) were unable to reduce the degree of creatinuria in exophthalmic goiter by giving sodium bicarbonate by mouth. From this they concluded that acidosis was not responsible for creatinuria. Palmer (1927), in a preliminary report, stated that the creatinuria of exophthalmic goiter could be markedly diminished by the administration of iodine. A complete report of this work was published by Palmer, Carson and Sloan in February, 1929. Included in the reports were 11 cases of adenomatous goiter with hyperthyroidism and 32 cases of exophthalmic goiter. It was found that "in all cases excreting appreciable amounts of creatin in the urine there is a marked diminution of the creatinuria following the administration of iodine," and that "the influence of iodine on the creatinuria is usually accompanied by a fall in basal metabolism, but not always."

After the publication of the report by Palmer, a similar study was started in the metabolism laboratories of The Mayo Clinic.

**Method of Study and Results.** Creatin was determined by the method of Benedict, and creatinin by the method of Folin. All analyses were made in duplicate. Both creatin and creatinin were calculated and expressed as nitrogen. The cases were divided into 3 groups.

**GROUP 1.** This group served as a control and consisted of 274 patients (76 males and 198 females) from whom samples of urine were taken. These patients represented the general run of those who register at the clinic, with the exception that patients with hyperthyroidism were excluded. The urine was examined only for the presence or absence of creatin, in order to determine the frequency of creatinuria in conditions other than hyperthyroidism. Since in this group the specimens of urine were not collected over a period of 24 hours, all calculations in the data were made on the basis of 1 liter of urine. Unless the amount of creatin calculated as nitrogen exceeded 0.02 gm. in each liter, the urine was considered to be free of creatin. When the calculated amount of creatin nitrogen was more than 0.02 gm. but less than 0.04 gm. the urine was considered to contain traces of creatin; it was considered to contain definite amounts when the calculated nitrogen exceeded 0.04 gm. but was less than 0.1 gm., and marked amounts when the calculated nitrogen exceeded 0.1 gm. In some instances when creatin was found only in traces probably creatin was actually present in the urine; in other instances creatin was probably absent, and the amount determined represented unavoidable technical errors due to the limitations of the method.

Traces of creatin were found in the urine of 7 of the 76 male patients (9 per cent). Only 1 patient showed more than a trace; this was a boy aged eleven years.

Traces of creatin were found in the urine of 17 of the 198 female patients (9 per cent); it was found in definite amounts in 13 patients (7 per cent), and in marked amounts in 14 patients (7 per cent), making a total of 23 per cent including those showing traces, or 14 per cent excluding those showing traces. The creatinuria in these women occurred in definite or marked amounts in the following conditions: arthritis, 4 cases; cholecystitis, 3 cases; constipation, 1 case; hypertension, 2 cases; indeterminate, 2 cases; intra-ocular tumor, 2 cases; gumma of leg, 1 case; migraine, 2 cases; normal woman, 1 case; neurosis, 2 cases; obesity, 2 cases; pituitary tumor, 1 case; pregnancy, 2 cases; scleroderma, 1 case, and uterine fibromyoma, 1 case. In some instances the creatinuria may possibly have been a concomitant of the disease; in others, it represented merely the not infrequent creatinuria occurring in women.

GROUP 2. This group consisted of 154 patients taken at random from those treated in the hospital for goiter. Nine of these patients did not have hyperthyroidism. The group included cases of exophthalmic goiter, adenomatous goiter with hyperthyroidism and adenomatous goiter without hyperthyroidism. Many of the patients had been treated with iodine before admission to the hospital. The urine in these cases was examined once or twice immediately after admission, to determine the presence or absence of creatin. As in Group 1, creatin was not considered to be present unless the amount, calculated as nitrogen, exceeded 0.02 gm. in each liter of urine. Tables 1 and 2 show the results obtained in this group. One hundred fifteen patients had exophthalmic goiter; 39 of these were males. Thirty patients had adenomatous goiter with hyperthyroidism; 5 of these were males. Nine patients had adenomatous goiter without hyperthyroidism; all were females.

Table 1 shows that of 25 untreated female patients with exophthalmic goiter, 21 (84 per cent) had demonstrable creatinuria and that of 8 men similarly affected, all had creatinuria. In the entire series of 115 patients with exophthalmic goiter 60 per cent of the males and 62 per cent of the females showed the presence of creatin, regardless of the fact that nearly two-thirds had been given iodine for several days and that some had received iodine for as long as a month. The incidence of creatinuria was less in those patients who were under treatment with iodine, although the decrease cannot be said to be closely related to the length of time of administration.

The incidence of creatinuria in cases of adenomatous goiter with hyperthyroidism is shown. Two of the 5 males (40 per cent) had creatinuria and 17 of the 25 females (68 per cent) had creatinuria. Creatinuria was demonstrated in 19 (63 per cent) of the total number, an incidence slightly more than that occurring in the entire

group of exophthalmic goiter but not as high as in the untreated cases of exophthalmic goiter.

TABLE 1.—INCIDENCE OF CREATINURIA IN GROUP 2.

	Exophthalmic goiter; administration of compound solution of iodine, days.						Adenomatous goiter.		
	None.	1 to 3.	4 to 7.	7 to 14.	14 to 30.	More than 30.	Total.	With hyperthyroidism.	Without hyperthyroidism.
Males:									
With creatinuria . . . .	8	3	5	2	1	4	23	2	
Without creatinuria . . . .	...	3	6	4	3	...	16	3	
Per cent with creatinuria .	100	50	45	33	25	100	60	40	
Females:									
With creatinuria . . . .	21	10	7	5	2	2	47	17	1
Without creatinuria . . . .	4	2	10	5	5	3	29	8	8
Per cent with creatinuria .	84	80	41	50	30	40	62	68	11
Total:									
With creatinuria . . . .	29	13	12	7	3	6	70	19	
Without creatinuria . . . .	4	5	16	9	8	3	45	11	
Per cent with creatinuria .	87	72	43	44	27	67	61	63	

The fact that in exophthalmic goiter the incidence of creatinuria was 61 per cent, and in adenomatous goiter with hyperthyroidism, 63 per cent, while in the control group it was only 9 per cent in males and 23 per cent in females, indicates that creatinuria can be considered as a fairly common and characteristic phenomenon of hyperthyroidism. The incidence of creatinuria in females with adenomatous goiter without hyperthyroidism was only 11 per cent.

A comparison of the duration of the disease with the incidence of creatinuria in untreated exophthalmic goiter was made, but on account of the irregularity of the results and the relatively small number of cases conclusions could not be drawn. It was evident that age is probably not a determining factor in the production of creatinuria in adult patients with exophthalmic goiter. Palmer, likewise, did not find correlation between the excretion of creatin and the age of the patients in his cases of exophthalmic goiter.

In Table 2 the basal metabolic rate is compared with the intensity of the creatinuria in cases of exophthalmic goiter in which treatment was not given. It is seen that there is not a strict parallelism between the basal metabolic rate and the amount of creatin excreted; yet it is equally evident that the amount of creatin excreted by a group of patients whose metabolic rates were very high was much greater than in a group whose metabolic rates were low.

GROUP 3. This group consisted of 10 patients who had frank exophthalmic goiter. Daily 24-hour specimens of urine from the

time of admission to the time of dismissal of each patient were examined. The routine treatment for exophthalmic goiter employed at the clinic was given to all of these patients. The diet was not restricted to food free from creatin. Compound solution of iodine was given in doses of 30 minims daily, except in one instance (Case 1, Table 3) in which 100 minims were given daily for the first 4 days. The purpose of this part of the study was to determine the effect of iodine on the excretion of creatin. Nine of the 10 patients underwent thyroidectomy and, incidentally, the effect of thyroidectomy on excretion of creatin was determined in these 9 cases. The patients in this group were not under such close supervision as is necessary for conducting complete metabolic experiments, and the specimens of urine obtained were somewhat irregular and incomplete. Because of this irregularity the percentage of the total creatinin nitrogen which appeared as creatin nitrogen is of more significance than the absolute amounts of these substances. The failure of the patient to empty the bladder at a stated time each day and the incompleteness of some of the specimens of urine undoubtedly accounts, in large part, for the variations in the output of preformed creatinin nitrogen.

TABLE 2.—RELATION OF INITIAL BASAL METABOLIC RATE TO AMOUNT OF CREATIN EXCRETED IN EXOPHTHALMIC GOITER NOT TREATED WITH IODINE (GROUP 2).

Sex.	Basal metabolic rate, per cent.	Creatin in each liter, gm.	Sex.	Basal metabolic rate, per cent.	Creatin in each liter, gm.
M . . . . .	+13	0.04	F . . . . .	+44	0.00
M . . . . .	+35	0.05	F . . . . .	+46	0.24
M . . . . .	+44	0.03	F . . . . .	+47	0.11
M . . . . .	+47	0.03	F . . . . .	+51	0.21
M . . . . .	+56	0.04	F . . . . .	+51	0.06
M . . . . .	+68	0.20	F . . . . .	+54	0.07
M . . . . .	+83	0.28	F . . . . .	+56	0.08
M . . . . .	+110	0.11	F . . . . .	+57	0.00
F . . . . .	+8	0.10	F . . . . .	+59	0.09
F . . . . .	+25	0.01	F . . . . .	+59	0.11
F . . . . .	+26	0.30	F . . . . .	+61	0.03
F . . . . .	+28	0.09	F . . . . .	+63	0.11
F . . . . .	+29	0.17	F . . . . .	+63	0.24
F . . . . .	+32	0.07	F . . . . .	+68	0.25
F . . . . .	+37	0.03	F . . . . .	+68	0.12
F . . . . .	+40	0.00	F . . . . .	+88	0.14
F . . . . .	+42	0.04			

The data presented in Table 3, from 4 representative cases, confirm the observation of Palmer that as patients with exophthalmic goiter improve following the administration of iodine, a decrease in the amount of creatin excreted occurs. Generally the decrease was noticeable within the first 3 days and was marked by the end of a week, when creatin had practically disappeared from the urine. In 5 of 9 cases the creatin appeared for a few days following thyroidectomy, even with the continued administration of iodine. In 3

patients the amount of creatin excreted postoperatively exceeded the initial amount excreted before iodine was given. It is not known whether the postoperative creatinuria bears any relation to the severity of the postoperative reaction.

TABLE 3.—REDUCTION OF CREATINURIA IN EXOPHTHALMIC GOITER FOLLOWING THE ADMINISTRATION OF COMPOUND SOLUTION OF IODINE (GROUP 3).

Case.	Age. Sex.	Diagnosis.	Date.	Basal metabolic rate, per cent.	Total creatinin nitrogen, gm.	Preformed creatinin nitrogen, gm.	Creatin nitrogen, gm.	Creatin nitrogen in amount of total creatinin nitrogen, per cent.
1 . .	56 F	Exophthalmic goiter patient in crisis	4-7*	+64	0.26	0.10	0.16	62
			4-8	....	0.29	0.12	0.17	59
			4-9	....	0.29	0.12	0.17	59
			4-10	....	0.25	0.13	0.12	48
			4-11	....	0.29	0.19	0.10	34
			4-12	....	0.21	0.16	0.05	24
			4-13	+43	0.28	0.18	0.10	36
			4-14	....	0.16	0.15	0.01	6
			4-15	....	0.20	0.20	None	None
			4-16	....	0.20	0.20	None	None
			4-17	+34	0.13	0.13	None	None
			4-18	....	0.12	0.12	None	None
			4-19	....	0.13	0.13	None	None
			4-20	....	0.21	0.21	None	None
			Returned home for 10 days					
			4-30	+52	0.10	0.10	None	None
			5-1	....	0.16	0.16	None	None
			5-2†	....	0.17	0.17	None	None
			5-3	....	0.22	0.16	0.06	27
			5-4	....	0.29	0.23	0.06	21
			5-5	....	0.49	0.25	0.24	49
			5-6	....	0.25	0.15	0.10	40
			5-7	....	0.25	0.15	0.10	40
			5-8	....	0.18	0.18	None	None
			5-9	....	0.19	0.19	None	None
			5-10	....	0.24	0.24	None	None
2 . .	33 F	Exophthalmic goiter (patient moderately ill)	4-12	+49				
			4-17*	+45				
			4-18	....	0.37	0.20	0.17	46
			4-19	....	0.33	0.20	0.13	39
			4-20	....	0.28	0.19	0.09	32
			4-21	....	0.25	0.16	0.09	36
			4-22	+32	0.31	0.22	0.09	29
			4-23	....	0.31	0.22	0.09	29
			4-24	....	0.25	0.22	0.03	12
			4-25	....	0.25	0.22	0.03	12
			4-26†	....	0.24	0.19	0.05	21
			4-27	....	0.21	0.16	0.05	24
			4-28	....	0.44	0.19	0.25	57
			4-29	....	0.35	0.20	0.15	43
			5-1	....	0.30	0.24	0.06	20
			5-2	....	0.18	0.18	None	None
			5-3	....	0.15	0.15	None	None
			5-4	....	0.19	0.19	None	None

\* Administration of iodine started.

† Thyroidectomy performed.



TABLE 3.—REDUCTION OF CREATINURIA IN EXOPHTHALMIC GOITER FOLLOWING THE ADMINISTRATION OF COMPOUND SOLUTION OF IODIN (GROUP 3.)—Continued.

Case.	Age. Sex.	Diagnosis.	Date.	Basal metabolic rate, per cent.	Total creatinin nitrogen, gm.	Preformed creatinin nitrogen, gm.	Creatin nitrogen, gm.	Creatin nitrogen in amount of total creatinin nitrogen, per cent.
3 . .	50 F	Exophthalmic goiter (patient moderately ill)	4-17*	+46				
			4-18	....	0.35	0.30	0.05	14
			4-19	....	0.21	0.18	0.03	14
			4-20	....	0.36	0.27	0.09	25
			4-21	....	0.32	0.17	0.15	47
			4-22	+35	0.29	0.23	0.06	21
			4-23	....	0.29	0.23	0.06	21
			4-24	....	0.19	0.19	None	None
			4-25	....	0.21	0.21	None	None
			4-26	....	0.21	0.21	None	None
			4-27	+38	0.13	0.13	None	None
			4-28	....	0.23	0.22	0.01	4
			4-29	....	0.24	0.24	None	None
			4-30	....	0.24	0.24	None	None
			5-1	....	0.19	0.19	None	None
			5-2†	....	0.17	0.17	None	None
			5-3	....	0.37	0.26	0.11	30
			5-4	....	0.36	0.24	0.12	33
			5-5	....	0.32	0.26	0.06	19
			5-6	....	0.22	0.21	0.01	5
			5-7	....	0.22	0.21	0.01	5
			5-8	....	0.23	0.23	None	None
			5-9	....	0.11	0.11	None	None†
4 . .	44 M	Exophthalmic goiter (patient severely ill)	5-8*					
			5-9	....	0.51	0.31	0.20	39
			5-10	+103	0.46	0.30	0.16	35
			5-11	....	0.58	0.29	0.29	50
			5-12	....	0.34	0.18	0.16	47
			5-13	....	0.39	0.25	0.14	36
			5-14	....	0.39	0.25	0.14	36
			5-15	+94	0.24	0.17	0.07	29
			5-16	....	0.36	0.33	0.03	8
			5-17	....	0.24	0.24	None	None
			5-18	+91	0.29	0.29	None	None
			5-19	....	0.27	0.26	0.01	4
			5-20	....	0.31	0.31	None	None
			5-22	....	0.33	0.33	None	None
			5-23	....	0.23	0.23	None	None
			5-24	....	0.29	0.29	None	None
			5-25†	....	0.24	0.23	0.01	4
			5-26	....	0.18	0.18	None	None
			5-27	....	0.49	0.32	0.17	35
			5-28	....	0.49	0.28	0.21	43
			5-30	....	0.38	0.30	0.08	21
			5-31	....	0.24	0.24	None	None

\* Administration of iodine started.

† Thyroidectomy performed.

‡ Incomplete.

The basal metabolic rate may or may not decline parallel with the decrease in the amount of creatin excreted. Palmer was also unable to establish any constant relation between the metabolic rate and the amount of creatin excreted.

**Summary.** In a series of 145 cases of hyperthyroidism composed of 115 cases of exophthalmic goiter and 30 cases of adenomatous goiter with hyperthyroidism, creatinuria occurred in 89 cases (61 per cent). The incidence of creatinuria in exophthalmic goiter was 61 per cent and in adenomatous goiter with hyperthyroidism, 63 per cent.

Of 25 female patients with exophthalmic goiter not treated with iodine, creatin was found in the urine of 21 (84 per cent); of 8 men similarly affected and not treated with iodine, creatinuria occurred in all 8.

In a control group of 274 patients not having disease of the thyroid gland, creatin was found in marked or definite amounts in the urine of 14 per cent of the women; in an additional 9 per cent, traces of creatin were found. Creatin in definite or marked amounts was not found in the urine of any of the men; in 9 per cent of the men traces of creatin were found.

Palmer's observation on the effect of the administration of iodine in reducing the amount of creatin excreted by patients with exophthalmic goiter was confirmed. However, the assumption that the reduction of creatinuria is a specific effect of iodine is not justified, as it is equally as logical to assume that the diminished excretion of creatin occurs as a result of the improvement in the general health of patients with exophthalmic goiter which follows the administration of iodine.

For a few days immediately after thyroidectomy the excretion of creatin in exophthalmic goiter may increase in amount or occur when it has been previously absent, even though the administration of iodine is continued.

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## HEREDITARY AND FAMILIAL DIABETES MELLITUS.

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HEREDITY has been recognized as an etiologic factor in the causation of diabetes mellitus since the time of Rondelet, of Montpellier, in the early sixteenth century.

CHART I.—FAMILIAL AND HEREDITARY OCCURRENCE IN DIABETES.

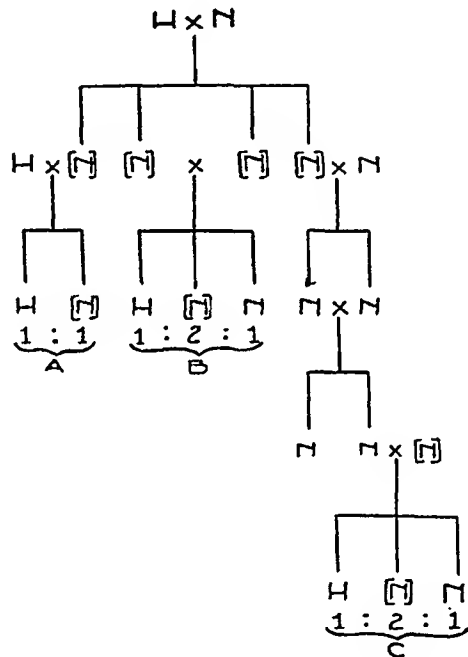
	Year.	Cases studied.	Per cent occurrence.
Schmitz <sup>1</sup>	1874	..	21.1
Frerichs <sup>2</sup>	1884	400	9.75
Flint <sup>3</sup>	1886	..	27.7
Zimmer <sup>4</sup>	1889	..	10.6
Seegen <sup>5</sup>	1893	..	14.0
Grube <sup>6</sup>	1895	..	7.9
Wegeli <sup>7</sup>	1895	..	29.0*
Fitz, Joslin <sup>8</sup>	1898	..	23.8
Bouchard <sup>9</sup>	1899	..	25.0
Kulz <sup>10</sup>	..	692	21.6
Williamson <sup>11</sup>	..	500	22.0
Pleasants <sup>12</sup>	1900	..	5.3
Naunyn <sup>13</sup>	1906	398	17.0
Von Noorden <sup>14</sup>	1917	..	25.4
Hoogslag <sup>15</sup>	1922	..	43.0
Montoro <sup>16</sup>	1924	400	18.0
Seckel <sup>17</sup>	1925	391	26.4
John <sup>18</sup>	1927	1000	9.7
Joslin <sup>19</sup>	1923	2800	21.0
Joslin <sup>19</sup>	1927	2646	25.5
Cammidge <sup>20</sup>	1928	800	28.0

\* Children.

Of 21 of the more important statistical reports dealing with this subject 13 give percentages of occurrence of familial and hereditary diabetes as over 21 per cent. John's figures of 9.7 per cent are the lowest we have noted for 30 years.

That the factor of heredity plays an important part as an etiologic consideration in the causation of diabetes in children, is well demonstrated by the experience of Joslin and Marble.<sup>21</sup> In the series of 12 diabetic children who had lived for 10 years or more there was an actual hereditary or familial history in 84.9 per cent. In their 200 living cases the incidence was 31.5 per cent, whereas in their 195 fatal cases the incidence was 21 per cent, essentially the same figure as found by Joslin in his entire series. Joslin recently observed, on the basis of these and other figures, that the longer diabetic children lived the more common hereditary factors became, merely because more time was allowed for others in the family to

develop the disease. Brief mention of some of the instances of familial or hereditary diabetes which have been reported since the time of Rondelet should be made. I have included only families in which 4 or more cases developed. Morton<sup>22</sup> reported 4 diabetic children in a family of 7 in 1696, Isenflamm<sup>23</sup> reported 7 cases in one family in 1784, Storer<sup>24</sup> (1798) reported 4 cases in one family, Fardel<sup>25</sup> 6 cases, Mosler<sup>26</sup> 6 cases, Roberts<sup>27</sup> 8 cases, Pavy<sup>28</sup> 6 cases, Flint<sup>29</sup> 6 cases, Frew<sup>30</sup> 4 cases, Fitz<sup>31</sup> 13 cases (patient had 2 diabetic wives), Neumann<sup>32</sup> 6 cases, Pribram<sup>33</sup> 5 cases and 1 doubtful case, Heiberg<sup>34</sup> 6 cases, Allen and Mitchell<sup>35</sup> 8 cases, Foster<sup>36</sup> 4 cases in one family, 4 cases in another family, Langaker<sup>37</sup> 5 cases, Joslin<sup>38</sup> 14 cases in one family, 8 cases in another family and Kennedy<sup>39</sup> 10 cases. In 1859 Griessinger<sup>40</sup> could only find 3 instances in the literature of familial diabetes.<sup>22,23,24</sup>



H—High Blood Sugar. N—Normal Blood Sugar  
 [N]—Heterozygous Normal (hybrid carriers)

CHART II.—Experimental breeding of mice (Cambridge).

Since many cases of diabetes have, no doubt, escaped diagnosis throughout the life span of the patient, and since it is really unusual in the United States for a patient to know any details concerning his ancestors of several generations, or even his slightly distant relatives, complete hereditary charts are difficult to obtain. Physical characteristics have often been shown to follow, in general, the Mendelian law of heredity, but it remained for Howard and Cam-

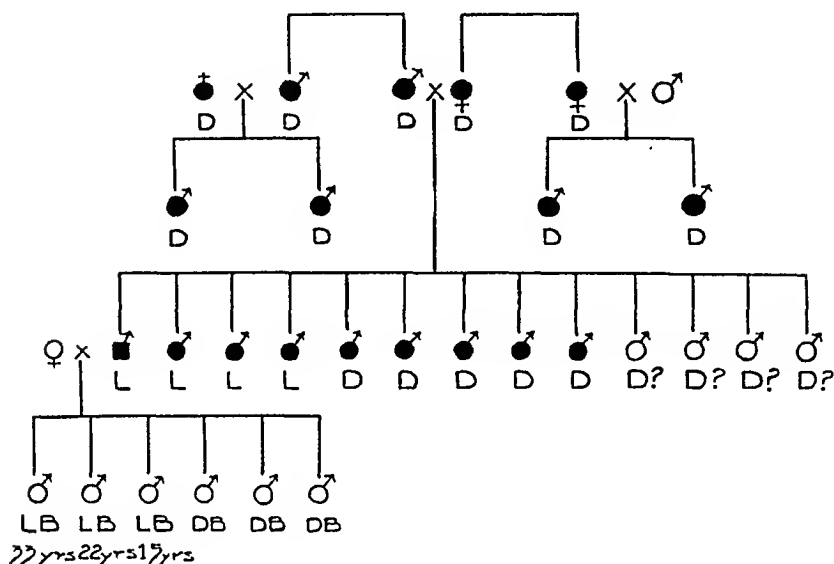
midge,<sup>41</sup> in England, to demonstrate for the first time experimentally the transmission of a chemical characteristic according to the Mendelian law.

These workers found that if certain mice having a high fasting blood sugar (116 to 120 mg. per cent) were mated they produced offspring having the same high blood sugar, but if mice having these high blood sugars were crossed with mice having normal blood sugars (about 85 mg. per cent) all of the progeny possessed normal blood sugars. One could conclude that in these experiments the high blood sugar played the part of the recessive characteristic. When these seemingly normal offspring were crossed with high blood sugar mice the results followed the Mendelian law, namely, there were equal numbers of high blood sugar mice and seemingly normal mice or hybrid carriers. If the seemingly normal mice (hybrid carriers) were mated with each other the progeny had high and normal blood sugars in the proportion of 1 to 3. This demonstrated that the heterozygous normal or hybrid carriers, although apparently normal were capable of transmitting the characteristic to their offspring with results following the Mendelian law.

Cambridge and Howard further found that if they mated their hybrid carriers with true normals from another stock all of the offspring had normal blood sugars. If these were again mated with true normals the progeny were apparently normals. This could be repeated through many generations with identical results, but if 2 related offspring from such crossings were mated, or if 1 of these mice was mated with another mouse with similar ancestry, some of the progeny would show a high blood sugar in the proportion of 1 to 3. It could then be demonstrated that 2 of the remaining 3 mice were hybrid carriers, and that only 1 was normal and incapable of transmitting the chemical characteristic. This proved how easily a characteristic might be recessive and remain hidden for many generations only to show when the proper mating qualifications were met. If further workers substantiate this work it appears of great significance, since it not only clearly demonstrates the transmission of a certain tendency to a specific blood sugar level, but also suggests that future experiments may determine that other chemical constituents of the blood may follow the law of Mendel.

Cambridge<sup>20</sup> later found similar results while using other animals and also reported a series of cases of diabetes mellitus in English families wherein the same laws were followed. In this latter study he was especially fortunately situated, since we in America find it much more difficult to find families who have adequate knowledge of their ancestry. He found that in the cases where the disease was transmitted as a dominant characteristic the course of the disease was found to be mild, whereas in the cases where the characteristic was recessive the course was usually grave from the onset.

It is my object to present below a series of cases of interest from the viewpoint of hereditary and familial diabetes mellitus. Most of these patients were seen in the Metabolic Clinic of the New York Post-Graduate Hospital. Several were seen in private practice.



Patient ■ Affected Males ♂ Unaffected Males ♂  
 Unaffected Females ♀ Living - L Dead - D  
 Diabetic History Unknown - ? Hemophilic - B

CHART III.—Hereditary and familial chart of patient J. F.

NOTE.—Dominance of diabetes mellitus. Dominance of male offspring. Although patient's offspring have thus far failed to develop diabetes, they have all been bleeders, 2 having died from hemorrhage after tonsillectomy.

**Case Reports.** CASE 1.—J. F. The accompanying hereditary chart shows an unusual dominance of the disease, but the results are what one should anticipate following the mating of two diabetics, especially if the disease was a dominant characteristic in them. The patient, aged 59 years, was a Hebrew. His occupation was that of a candy machine salesman. He used alcohol to excess. There was no serologic evidence of syphilis. At the time he was first seen in the Metabolic Clinic of the Post-Graduate Hospital, October 24, 1929, he had diabetes mellitus of 18 years' duration. He was also suffering from an atrophic polyarthritis of 3 years' duration and early cardiac failure of 6 months' duration. During the first 16 years of his illness he had taken large doses of alkalis (50 to 100 gm. of various kinds a day). During the past 2 years he had tried insulin twice but had frequently hypoglycemic reactions, so discontinued its use. Two months preceding admission he fell from a wagon, lacerating his scalp. This wound became infected, which brought him to the hospital. Three years before admission he weighed 195 pounds, although he was only 5 feet 5 inches tall (marked obesity). Six months before admission he weighed 165 pounds and at the time of admission 120 pounds.

*Physical Examination.* Positive findings on admission:

*Head*—infection infiltrating soft tissues over most of frontal region. *Pupils*—react sluggishly to light; left pupil larger than right. *Tonsils*—large and obviously infected. *Gums*—edentulous except for a few old roots; marked pyorrhea. *Neck*—small, shotty cervical lymph nodes, also felt in left inguinal and right epitrochlear regions. *Chest*—emphysematous in type with usual accompanying signs. *Heart*—sounds of poor quality; rhythm irregular with frequent premature beats; rate average, 85; moderate enlargement to the left in the third, fourth and fifth interspaces, A2 greater than P2; no murmurs heard. *Abdomen*—normal; liver at costal margin. *Reflexes*—all deep reflexes markedly diminished; knee jerks and Achilles reflexes could not be elicited. No pathologic reflexes were noted. *Fundi*—high hyperopia; both eyes showed soft exudates at the macula.

*Course in Hospital.* On admission a casual specimen of urine showed 9.5 per cent sugar. He was placed on a diet containing carbohydrate, 60 gm., protein, 45 gm., fat, 105 gm. (total calories, 1407) (Mosenthal Diabetic Diet No. 3), and was given insulin, 40 units, daily, in divided doses. He became sugar-free quickly and the insulin was reduced to 20 units in five days and discontinued in 15 days, because the patient was then having frequent hypoglycemic reactions. The infection had meanwhile cleared up. Five days after admission his heart suddenly gave evidence of failure, the liver border showing 3 fingerbreadths below the costal margin. Digitalization by moderate dosage was begun. Three days later Cheyne-Stokes breathing was noted while the patient was asleep, which ceased when he was awakened. After a thorough neurologic examination Dr. Sherwood concluded that there was no evidence of intracranial pathology; that the reflex changes were due to a diabetic polyneuritis. The following day the heart became regular and the patient was discharged in 3 weeks, November 25, 1929, on a dosage of tincture of digitalis, 20 minims t.i.d., and a diet of carbohydrate, 80 gm., protein, 60 gm., fat, 140 gm. (total calories, 1876) (Mosenthal Diabetic Diet No. 4). No insulin was then required. A summary of his laboratory findings accompanies.

#### LABORATORY FINDINGS, BLOOD CHEMISTRY.

Date.	Sugar, mg. per cent.	Cholesterol.	Uric acid.	Urea.	Creatinin.	CO, combining power.
Oct. 14, 1929 . . .	0.256	0.169	...	31.2	...	43.8
Oct. 25, 1929 . . .	0.089	0.188	4.0	25.0	2.3	47.5
Nov. 1, 1929 . . .	0.163	0.200	...	22.0	...	...
Nov. 4, 1929 . . .	0.150	...	...	...	...	42.8
Nov. 11, 1929 . . .	0.096	...	...	...	...	...
Nov. 22, 1929 . . .	0.275	...	...	...	...	62.6
Dec. 20, 1929 . . .	0.120	0.204	...	...	...	53.2
Mar. 12, 1930 . . .	0.138	0.152	...	18.3	...	46.6
Mar. 21, 1930 . . .	0.286	...	4.4	18.3	...	45.0
Mar. 25, 1930 . . .	0.109	...	...	23.2	...	47.5

NOTE.—There seems to be no relationship between the blood sugar and cholesterol levels.

December 5, 1929. The patient suddenly developed a complete right homonymous hemianopsia. This cleared up gradually and completely by December 19, 1929. At the latter date the patient was readmitted, having gained from 133 to 162 pounds in 14 days with the development of marked edema and ascites. On December 5, 1929, he was on the above-mentioned

diabetic No. 4 diet and showed 4.2 per cent sugar in a 24-hour specimen of urine. A curious phenomenon then took place. As his edema increased he violated his diet, eating all kinds of carbohydrate foods and even taking sugar on his food and in his coffee. In spite of that intake of carbohydrate with the increase in edema the urinary sugar dropped to negative as measured by the Benedict qualitative test, the fasting blood sugar being as low as 0.12 per cent. This took place without the use of insulin. He was discharged in good condition in 1 week and returned, March 12, 1930, again decompensated. Once more he was discharged in good condition and has not returned for further treatment.

*Spinal Fluid.* Wassermann, 0. Colloidal-gold curve, 11232100000. Cell count, 1 lymphocyte. Butyric acid test, 1+.

*Blood Wassermann Test.* Negative.

*Blood Count.* Slight secondary anemia otherwise normal throughout.

*Urine.* Specific gravity varied from 1.029 to 1.011. Reaction, acid throughout. Sugar, 9.4 to 0 per cent. Diacetic acid and acetone were absent throughout. Albumin absent during the first admission; 1+ during all later admissions.

The blood pressure varied from 122 systolic and 70 diastolic to 92 systolic and 60 diastolic.

*Discussion.* Certain points are of great interest and importance in the above history. The outstanding feature is the unquestionable transmission of the tendency toward the development of diabetes as a dominant characteristic. The history was attested by both the patient and his wife. The 4 brothers who died of a questionable condition died in Russia during the World War. We can conclude that the patient's diabetes was mild in character for 18 years and he stated that his relatives all had the disease for many years before dying. This is in accordance with Cammidge's statements in reference to instances where the disease is transmitted as the dominant characteristic. Another curious fact is that, although the patient's children have not as yet developed diabetes, they have been, without exception, bleeders (hemophiliacs), as diagnosed by physicians, and that 2 of them have died as a direct result of hemorrhage following tonsillectomy.

The neurologic findings have also been of interest. The finding of pseudotabes of diabetes, as determined by the absent or reduced knee jerks and Achilles tendon reflexes, was recognized simultaneously by Borehardt<sup>42</sup> and Althaus<sup>43</sup> in 1884. Since that time many studies have been made to determine the location of the lesion and the mechanism which produces it. Sandmeyer,<sup>44</sup> Naunyn<sup>45</sup> and Leyden and Goldscheider<sup>46</sup> believed that the process represented the combined sclerosis of pernicious anemia first described by Lichtheim.<sup>47</sup> Williamson, in a series of studies,<sup>48</sup> and Schweiger<sup>49</sup> concluded that the changes in the posterior column were secondary to degeneration in the intramedullary portion of the posterior roots; in other words, essentially, the same as in tabes dorsalis. Kraus<sup>50</sup> concluded that clinical evidence was in favor of a lesion proximal to the juncture of the roots. Charcot<sup>51</sup> felt that most diabetic disorders of this type must be due to peripheral neuritis. Woltman



and Wilder,<sup>52</sup> in a recent careful study of changes in the spinal cord and peripheral nerves of diabetics, found the spinal cord changes to be relatively unimportant as compared to the changes in the peripheral nerves. The location of the significant nervous lesions in these cases probably varies in different cases and hence no universal agreement can be reached.

The mechanism causing these changes is likewise undetermined. Grube<sup>53</sup> claimed to have observed marked neuritis after subcutaneous or intravenous injection of dextrose into rabbits but his work has not been confirmed. Auché<sup>54</sup> applied sugar locally and by injection to the sciatic nerves of guinea pigs and concluded that sugar was not the cause of degeneration. Eichhorst<sup>55</sup> kept the nerves of man and frog in solutions of dextrose, acetone and oxybutyric acid for several days with no effect.

The possibility of infection, so common in diabetics, as the etiologic factor was suggested by Patrick.<sup>56</sup> In the 10 cases reported by Woltman and Wilder<sup>52</sup> in which neuritic changes were marked the acetone and sugar were under careful control. It seems logical in agreement with these authors to feel that if sugar or acetone bodies were responsible for such changes they would be found more frequently in young, severe diabetics rather than in chronic mild cases. They are actually much more common in the latter group.

The sudden occurrence of the right homonymous hemianopsia with its subsequent rather rapid clearing up would incline us to think of this happening as a cerebral accident; either a minute hemorrhage or, more likely, a temporary anemia due to an arteriolar spasm—the area affected was probably in the left cortical visual area or the left visual tract central to the chiasm.

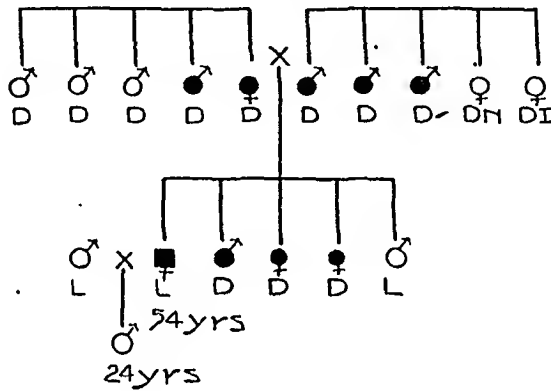
The third very interesting feature was the sudden increased tolerance for sugar with the onset of edema as noted above. That it was not due to a retention in the blood was shown by the low blood-sugar reading. At least three possibilities present themselves by way of explanation: (a) This patient had a past history of periods of seeming improvement. He then suffered from hypoglycemic reactions if he was taking insulin, although the dosage and diet might be unchanged. A similar phenomenon may have occurred coincidental with the onset of edema. (b) The carbohydrate tolerance may suddenly have been increased due to some other factor. (c) There may have been a retention of sugar in the tissues with the fluid. This is unlikely.

CASE 2.—E. P. The chart accompanying this history again presents the results of the mating of 2 known diabetics. Four of the 5 offspring have developed the disease and the fifth is still alive and may develop it.

The patient was a Jewess, aged 54 years. The past history, aside from diabetes and the usual diseases of childhood, was essentially negative. The blood Wassermann was negative. The disease had been discovered 10 years previously, when following a period of marked polydipsia the urine

was found to contain sugar. At that time the patient was obese, weighing 198 pounds. On examination she weighed 161 pounds. She had always been of a very nervous temperament. Her chief symptoms were: Weakness, 2 weeks' duration; polyuria, usually about  $3\frac{1}{2}$  quarts in 24 hours, 10 years' duration; polydipsia, more than 2 quarts a day; nocturia, once a night; polyphagia, moderate; furunculosis, subsiding on upper lip (on vulvæ 6 years previously).

The positive findings on *physical examination* were as follows: Unusual number of pigmented moles scattered over body; eyes, scleræ cloudy; fundi show marked tortuosity and sclerosis of arteries. Peripheral arteries, sclerotic. Blood pressure was 172 systolic and 90 diastolic to 160 systolic and 90 diastolic. Heart sounds of poor quality; area of precordial dullness enlarged. Apex, 12.5 cm. to the left of the midsternal line in the sixth interspace. The right border was 2 cm. to the right of the midsternal line. Lungs and abdomen negative. The knee jerks were absent.



### Code as in Chart III Nephritis-II Insanity-I

CHART IV.—Hereditary and familial chart of patient E. P. (Case 2.)

#### Laboratory Findings:

Blood chemistry.	February 24, 1930	May 19, 1930.
Urea nitrogen . . . . .	31.2	15.1
Creatinin . . . . .	1.4	
Sugar . . . . .	0.334	0.309
Cholesterol . . . . .	0.254	

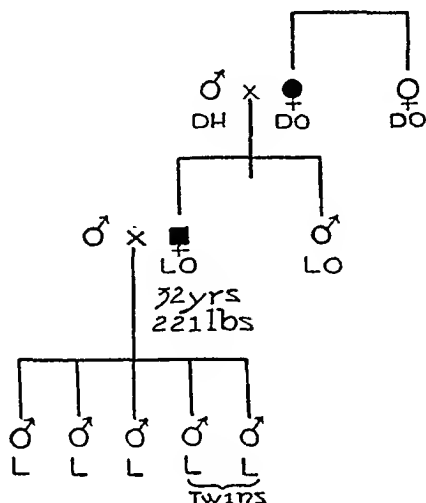
The urine was examined every 2 weeks for many months. The average findings were as follows: Specific gravity, 1.015 to 1.025; reaction, acid; sugar, faint trace to 1.43 per cent; albumin, 1+; acetone and diacetic acid, rarely 1+. The diabetes could be controlled by means of a qualitative diabetic diet, but the patient would not coöperate even to the extent of observing such a simple diet.

**Discussion.** As will be noted from the chart, diabetes mellitus was present in the families of both of the patient's parents' families in addition to being present in themselves. It would, therefore, be anticipated that a large proportion of the children would be likely to develop the disease if they lived long enough. As in the first case, the diabetes was mild in degree, having been present for 10



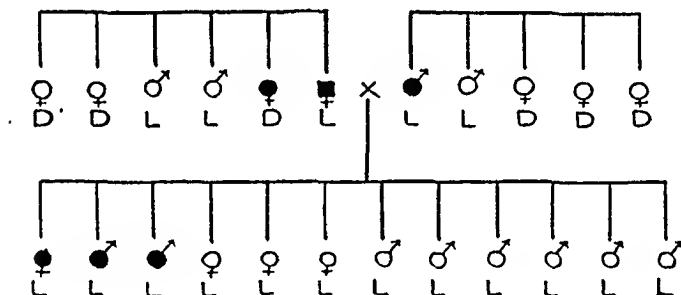
This patient improved quickly on a qualitative diabetic diet.

The remaining charts illustrate a number of instances in which there have been 3 or more cases of diabetes mellitus in an immediate family, except Chart VI, in which family obesity was very common.



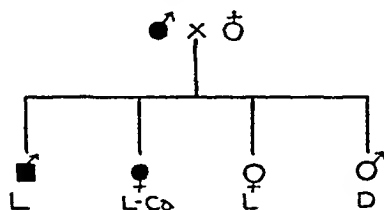
Code as in Chart III Obesity-O Heart disease-H  
Note prevalence of Obesity in this family

CHART VI.—Hereditary and familial chart of patient B. LaG.



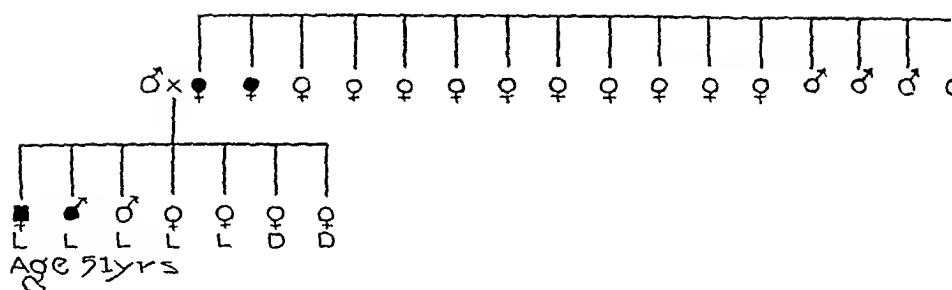
Code as in Chart III

CHART VII.—Hereditary and familial chart of patient M. C.



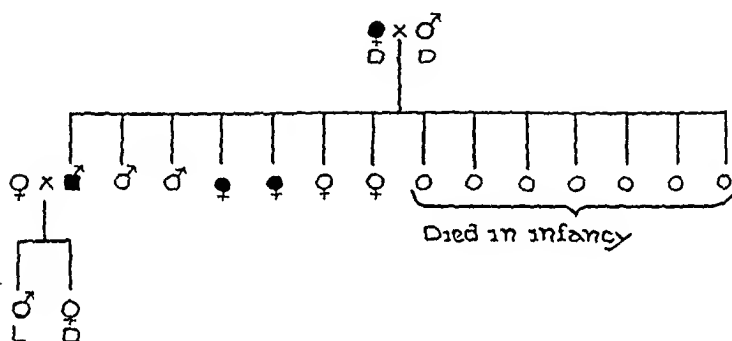
Code as in Chart III Cancer of the Breast-Ca

CHART VIII.—Hereditary and familial chart of patient A. B.



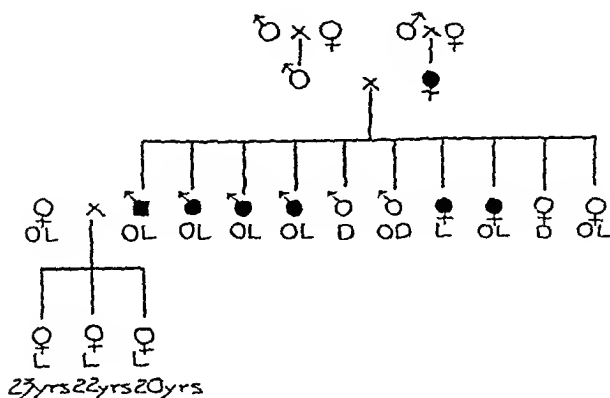
Code as in Chart III

CHART IX.—Hereditary and familial chart of patient C. S.



Code as in Chart III

CHART X.—Hereditary and familial chart of patient S. S.



Code as on previous charts

CHART XI.—Hereditary and familial diabetes mellitus, patient Z. K.

**Discussion.** It has not been my purpose to prove that all cases of diabetes mellitus are inherited or familial. It is, however, increasingly evident that these factors play a more important etiologic part than has hitherto been generally recognized. It is also possible that identical living conditions and dietary habits such as those resulting in obesity may be causative factors in producing more than 1 case of diabetes in a family. There are also many mild diabetics who are, no doubt, missed and hence omitted from the family trees as such.

There appear to be, then, two groups of factors which tend to produce diabetes mellitus in an individual. Hereditary tendency, H or h, and acquired factors, AF or af (infections, obesity, etc.). Diabetes mellitus is in many cases the product of the two factors. The same result is obtained whether the hereditary factor is large and the acquired factor is small or *vice versa*, hence:

$$H \times af = D$$

or

$$h \times AF = D$$

Needless to say, if the two groups of factors are both large the disease would theoretically be inevitable, while if they are both present but small, or if one is absent, the patient may never manifest evidence of the disease during life. Individuals in the last group are often discovered when blood-sugar determinations are made in the healthy members of a diabetic patient's family. Such a formula in its present form must not be used as an index of severity of the disease, but only as an index as to tendency to develop diabetes, *i. e.*,

$$H \times AF = D$$

might not develop into a severe case as other factors which we cannot evaluate at present must be introduced. A similar suggestion was made by Loeb<sup>57</sup> some years ago in reference to the etiology of cancer. Our cases have been in agreement with Cammidge's contention that when the characteristic was dominant the disease tended to be mild.

**Summary.** A tendency to high blood sugar can be transmitted according to the law of Mendel in mice and other animals. It is suggested that the disease diabetes mellitus can be transmitted according to the same laws in human beings. All cases of diabetes are probably not hereditary, but careful questioning will increase the incidence of this occurrence in the records of a series of cases. Certain cases are presented to illustrate and emphasize the hereditary and familial factor of diabetes in the human race.

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## INTERPRETATION OF FLARIMETER TESTS.

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THE physiology of flarimeter tests of circulatory fitness has been presented briefly by the authors in previous papers,<sup>1</sup> but many of those interested have not found it easy to apply these principles to the test in detail. The instrument that we have called the flarimeter has a large orifice for measuring vital capacity, and a small one for determining the degree, if any, of shortness of breath. The blows through each are made at a constant pressure of 20 mm. of mercury, by means of a sensitive water manometer. The ability of the heart and its coördinating mechanisms to adjust themselves to the strain imposed by the increased intrathoracic pressure and changes in the blood is estimated both by the length of blow through the small orifice and by the degree and rate of rise of blood pressure during the blow. We are studying these relationships in an effort



to add to or clarify, if possible, our knowledge of the causes of and variations in them (length of blow and blood pressure) and their significance. While wishing to avoid announcing premature opinions, the following general considerations must be thoroughly understood before attempting to interpret any flarimeter tests. Our own clinical experience to date is about 100 cases, while from selected field examiners we have received reports on 1044 adult males and 132 females, so that with those by unselected examiners, and those made at the Home Office, our experience covers well over 1500 cases. A brief analysis of this experience is presented.

**Empirical Normal Borderlines.** The nearest we can get to a typical test on a healthy adult male is to take the median\* value for each response. Only "first-class" risks, those without present or previous record of impairment were chosen, about 70 per cent of those given insurance at standard rates. Moreover, the only cases used were those from a small group of specially selected examiners, to exclude (as far as possible) errors of observation and technique. Home Office tests were also excluded to keep the series homogeneous. The results are shown in Fig. 1. Unfortunately, circumstances prevented using the standard exercise in many cases, in others the standard steps were used but not the standard number of ascents by age and weight, so that only 174 were given truly standard exercise. The final blow, 2 minutes after exercise, was so recently introduced that Tr refers to only 131 cases.

Under "Remarks" in Fig. 1 are shown the values tentatively adopted as "Normal," and the borderlines between "Normal" and "Abnormal." These do not refer to a particular blow but to the best of the three trials in each case. Thus, the median value of Tm is that of the longest blows in Test III taken from each report, and so must be longer than the medians for each blow. The longest T<sub>20</sub> of the three is similarly taken, but the value of S<sub>+</sub> is not necessarily the longest, as it must refer to the same blow as that from which Tm is taken. Round numbers are adopted as normal, and they are purposely made slightly severe because it is expected that performance will improve somewhat in the future.

The abnormal borderlines are so chosen that about 5 per cent of healthy adult males should fail to pass each border. This condition is met in vital capacity and in (Tm-S<sub>+</sub>), one of the measures of irritability, but the borderlines for shortness of breath appear to be too severe. The factor of personal performance, however, must not be forgotten, particularly in Te and Tr, the lengths of the blows after exercise in Test V, which result from single trials only. The effect of these borderlines for Tm and (Tm-S<sub>+</sub>), the best measures at present of shortness of breath and irritability, is compared with those of the diastolic pressure (at rest) in Table 1, on 500 cases in

\* One-half the values are on each side of the median, by definition.

FIG. 1.—MEDIAN VALUES FOR 470 "FIRST-CLASS" ADULT MALES.  
(By 70 selected examiners.)

I.		II.		III.			IV.	V.
At rest.		Vital capacity, Seconds.		Blows with small orifice (Blow 3, 388 cases).			At rest.	Standard exercise, small orifice blow (174 cases).
Pulse rate Systolic Diastolic	76	1.	21	1.	2.	3.	Rate Systolic	Pulse rate before No. of ascents
	120	2.	21	120	123	124		76 122
	76	3.	21	35	35	38	Diastolic	78 No. of bendings
				seconds Systolic Maximum systolic Total seconds	151 155	158		Length of blow, seconds
This line for Home Office use only		Per cent of normal	108	S <sub>+</sub>	47	50	52	Pulse rate, end of 2 minutes
					31	32	34	Length of blow, seconds
Remarks:								
		Symbol.	Median.	Normal (adopted).	Abnormal below (adopted).	Cases with abnormal response.	Definition.	
V	.	.	.	107%	90%	6%	Per cent of normal by height (table of Myers).	
T <sub>10</sub>	.	.	38 sec.	40 sec.	25 sec.	9%	Irritability.	
T <sub>m-S<sub>+</sub></sub>	.	.	20 sec.	20 sec.	0	5%	Time for systolic to rise 20 mm.	
T <sub>m</sub>	.	.	54 sec.	55 sec.	40 sec.	8%	S <sub>+</sub> = Total systolic rise.	
T <sub>10</sub>	.	.	19 sec.	20 sec.	15 sec.	10%	Maximum systolic—systolic before blow.	
T <sub>r</sub>	.	.	49 sec.	50 sec.	40 sec.	11%	Shortness of breath.	
	.	.					Length of blow before exercise.	
	.	.					Length of blow 10 seconds after exercise.	
	.	.					Length of blow 2 minutes after exercise.	

the first three columns, and (in the last column) on those in the first 1000 cases from which all impaired cases were excluded except those having nothing abnormal but arterial tension.

TABLE 1.—RELATIVE FREQUENCY OF ABNORMAL ARTERIAL TENSION, IRRITABILITY AND SHORTNESS OF BREATH—ADULT MALES.

Number of cases . . . . .	First 500 cases not rated for occupation.			Without impairment except arterial tension.
	Standard.	Rated.	Rejected.	
	298	94	108	738
Percentage of above numbers of cases with this impairment.				
Impairment.	Per cent.	Per cent.	Per cent.	Per cent.
Hypertension { Diastolic 100 or over	1	3	22	2
{ Diastolic 90 or over	15	20	38	12
Hypotension (diastolic under 60) . .	1	2	6	3
Irritability (Tm-S <sub>+</sub> negative) . . .	6	4	18	5
Shortness of breath (Tm under 40) .	9	15	30	8

Evidently shortness of breath as defined by failure to blow 40 seconds is more frequently encountered than cardiac irritability, as indicated by a rise in systolic pressure numerically greater than the length of the blow. Among insurable cases both irritability and shortness of breath are more frequent than abnormal diastolic pressure. Does this mean a poor choice of borderline, or is it of clinical significance? Not necessarily, because a short Tm by itself may not always indicate shortness of breath, for the three measures Tm, Te and Tr must check to be consistent. If they do not, the simplest explanation is poor performance in the short blows. Similarly, (Tm-S<sub>+</sub>) and T<sub>20</sub> should check. We must, therefore, class as consistently normal or abnormal only those cases in which the responses check, while reports with a single response abnormal must be considered as inconsistent. Such inconsistencies are inherent in all tests depending upon personal performance. To discount properly the factors of performance and emotion is an essential preliminary to the interpretation of flarimeter reports.

**Analysis of Responses.** A further study of the tests on first-class risks is presented in Table 2. Two-thirds (65 per cent) of the reports are consistently normal, that is, all the responses are above the abnormal borderlines, while nearly one-third; (29 per cent) are inconsistent. Most of the inconsistencies are in the "nonstandard" tests, and when they are further analyzed it is seen that 13.8 per cent, or nearly half the inconsistencies are in Tc. As most of the tests are "nonstandard" because the exercise given was thirty bending movements in 1 minute, evidently this produces more breathlessness than does the standard step exercise, although the return to normal is the same, for Tr fails in 1.7 per cent of each type of test.

TABLE 2.—ANALYSIS OF RESPONSES IN FLARIMETER TESTS.  
(By 70 selected examiners on 470 first-class male risks.)

Type of test.	Standard.		Non-standard.	Total.
Number of cases . . . . .	174		296	470
	Per cent.	Per cent.	Per cent.	
Percentage of above numbers of cases giving:				
1. Normal tests . . . . .	78		58	65
2. Consistently abnormal tests . . . . .	7		5	6
3. Inconsistent tests, total . . . . .	15		37	29
(a) Single response abnormal . . . . .	13		26	21
(b) Evidently inconsistent . . . . .	..		5	3
(c) Perfunctory performance . . . . .	2		6	5

Type of test.	Responses consistently abnormal.			Inconsistent single response Ab (3a).			Inconsistent (3b). (3c).	
	Stand-ard.	Non-stand-ard.	Total.	Stand-ard.	Non-stand-ard.	Total.	Non-stand-ard.	
Number of cases . . . . .	174	296	470	174	296	470	296	
<i>Per cent of cases with this response abnormal (in number of cases on line below).</i>								
Number of cases . . . . .	12	16	28	174	296	470	16	19
	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.
Subnormal.								
Rate (Test IV) . . . . .	25	12	18	0	0	0	6	5
Systolic (Test IV) . . . . .	0	0	0	0	0	0	6	0
Diastolic (Test IV) . . . . .	0	0	0	0	0	0	0	0
V . . . . .	17	31	25	4.6	1.4	2.6	12	37
T <sub>20</sub> . . . . .	0	88	50	0.6	6.4	4.3	31	5
T <sub>m</sub> -S <sub>+</sub> . . . . .	33	62	50	1.7	1.0	1.3	12	11
T <sub>m</sub> . . . . .	33	62	50	0	1.0	0.6	31	58
T <sub>e</sub> . . . . .	58	62	61	4.6	13.8	10.4	69	89
Tr . . . . .	100	50	93	1.7	1.7	1.7	31	

There are too many failures (4.6 per cent) in Te, even among the standard tests, but nevertheless we do not feel that 15 seconds is too severe a borderline, because considerable improvement in performance is to be expected. Moreover, shortness of breath should first appear immediately after exercise (Te), later 2 minutes after (Tr) and finally, when well established, even before exercise (Tm). With the borderlines adopted the failures do increase in the expected order. Among the eight standard tests (4.6 per cent) showing nothing abnormal but vital capacity, 6 showed underweight; in fact, the average underweight was 4 pounds, the average vital capacity 16 per cent below normal. This means body-build, as will be explained later.

The group "consistently abnormal" includes all cases in which two or more responses failed to rise above the borderlines, but which were not evidently inconsistent. The cases in this group were therefore short of breath, showed irritability, or the two combined. Twenty-eight (6 per cent) of first-class risks fall in this group, so that the odds are about 15 to 1 that a healthy adult male will not give a consistently abnormal report. Of course, some of the "first-class" risks may not be really first-class (without present or previous

impairment), and a closer study might reveal an impairment which has been overlooked but is indicated by the flarimeter test. The fact that, on the average, three or four responses are abnormal in each case lends color to this suspicion.

The large percentage (29) of inconsistent reports is to be expected. All the difficulties and possible failures of 70 beginners, most of whom never saw the technique demonstrated, are included. But errors of performance and technique are not the sole cause of inconsistent reports as undoubtedly some seeming inconsistencies now are not yet understood.

The values to be studied first in a flarimeter test are the pulse rates and blood pressures at rest (Tests I and IV). Table 1 suggests that there is no systematic change in normal cases, but a more detailed study shows that the pulse pressure usually increases when the diastolic falls, and *vice versa*, and these usual coördinations indicate no great change in the work of the heart but merely passing emotion. The diastolic is higher in Test IV in about one-third of the tests, and in these the pulse pressure is usually lower. When the changes are small it seems reasonable to assume that this indicates a return to rest from a more active state in Test I, but an excessive rise in diastolic, combined with a distinct fall in pulse pressure, suggests vasoconstriction coming to the relief of a fatiguing heart muscle with possibly impaired intracranial circulation. The large and small orifice blows of Tests II and III, however, should not fatigue the heart, and recovery should be complete by Test IV. Our results show that the normal range of emotional variation (up or down) can be taken as about 20 mm. systolic, 10 mm. diastolic, and 15 pulse beats per minute. These borderlines agree with the clinical experience of Stieglitz,<sup>2</sup> who suggests that emotional hypertension is likely to become permanent and lead to degenerative circulatory changes.

Now there are five values of the systolic at rest, including the baseline of Test III, and two of the diastolic. If all show hypertension, we must assume its presence. The same system of checking is applied to all flarimeter responses. Satisfactory interpretation is dependent on a religious observance of the time schedule. By comparing the responses in this way with a standard performance, each serves as a control on the others, and an estimate of circulatory fitness is obtained that must ultimately prove superior to present methods.

An analysis of over 1000 reports on adult males is shown in Table 3. Flarimeter reports were disregarded in the Company's action on the cases in this table. Cardiac impairments, blood pressure, urinary findings, toxic goiter and overweight were the only impairments included. First and second class under company action must not be confused with first and second class under flarimeter report. Standard risks have been subdivided into two

classes, "first-class," those without present or previous impairment, "second-class," those with impairments too minor to rate. "Normal" reports are those in which every response is above its abnormal borderline; these are subdivided into two classes, "first-class," those above the median in all responses, "second-class," the remaining normals.

TABLE 3.—COMPARISON OF FLARIMETER REPORTS WITH COMPANY ACTION.

(All adult male risks except those rated for occupation, by 70 selected examiners.)

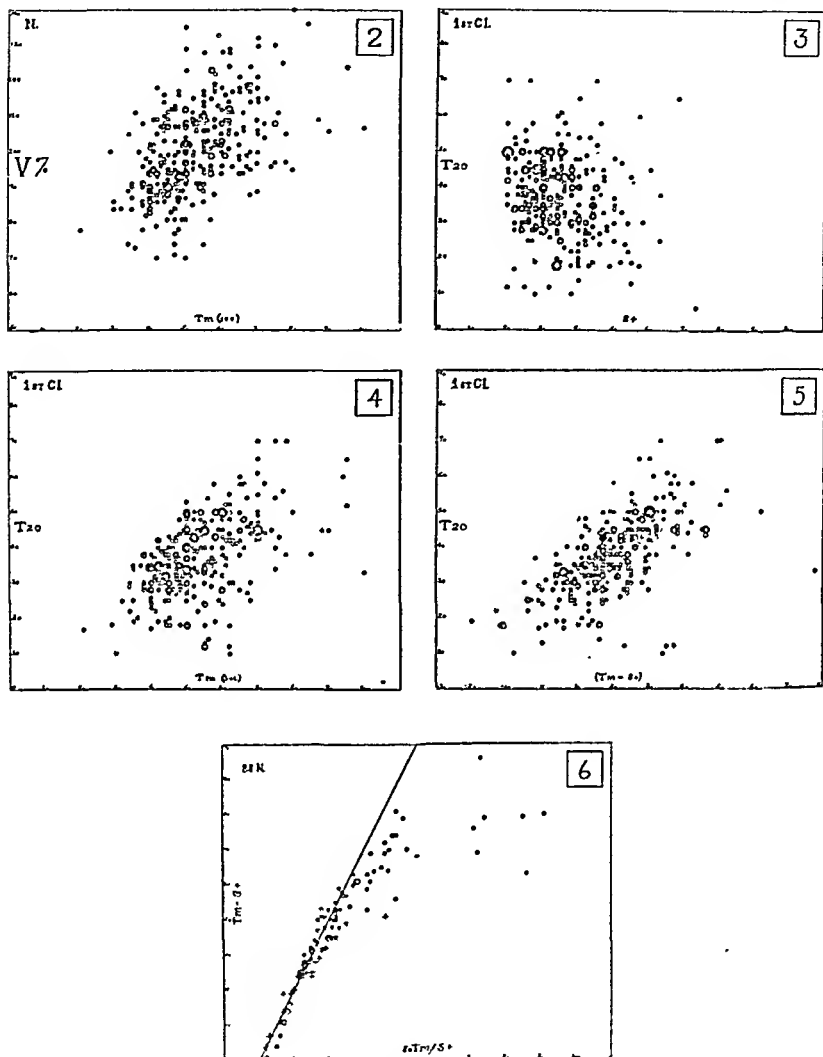
		Type of flarimeter report.							
		First-class.		Second-class.		Consistently abnormal.		Inconsistent.	
Company action.	Total cases.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
1. First-class .	490	86	18	218	44	29	6	157	32
2. Second-class .	207	36	17	105	51	12	6	54	26
3. Rated .	179	20	11	63	35	27	15	69	39
4. Rejected .	168	6	4	43	26	72	43	47	28
Total . . .	1044	148	14	429	41	140	13	327	31

The statistics indicate clearly that a normal flarimeter report is characteristic of a standard risk, for the frequency of second-class risks is maximum (51 per cent) for second-class reports. Only 6 per cent of first-class risks give consistently abnormal reports, which checks Table 2. Among the rejected risks it will be noted that but 4 per cent pass first-class tests, while 43 per cent give consistently abnormal reports. Thus, in spite of the large number of inconsistent responses, which include beginners' errors, perfunctory performance and types not yet numerous enough to classify, there can no longer be reasonable doubt that the flarimeter gives a real test of circulatory fitness.

The data on females are too few to define normals, as yet, but the first 132 give frequencies quite like Table 3 when the borderlines and medians for each response are taken as 5 points below those for males. Children show still shorter blows and a marked emotional instability, in the few cases studied.

**Correlation of Responses.** As reports began to accumulate in number, the empirical relations between the responses were reconnoitered by scatter diagrams. Over 40 of these were made on Home Office normals, first-class, standard, rated and rejected risks from the field, both male and female, for different pairs of responses. They showed positive correlation between  $V$  and  $T_m$  among the rated and rejected risks, and for all groups between  $T_m$  and  $T_{20}$ , while a negative correlation was shown between  $T_{20}$  and  $S_+$ . None of the groups showed any correlation between  $V$  and  $T_{20}$ ,  $V$  and  $S_+$ , or between  $T_m$  and  $S_+$ , although a positive correlation would be expected in the latter case, and undoubtedly would be found in successive tests upon a single subject, because the longer one blows the higher the systolic rises.

This early experience with the test indicated no correlation between vital capacity and length of small orifice blow among Home Office normals and standard risks, in agreement with Jackson



CORRELATION OF RESPONSES

Charts 3, 4 and 5 show that  $T_{20}$  is more closely related to  $(Tm - S_+)$  than to either  $(Tm)$  or  $S_+$ . Chart 6 shows that  $(Tm - S_+)$  is proportional to  $(20 Tm/S_+)$  near the abnormal borderline.

and Lees, but further data from selected examiners in the field gives a positive correlation of 49 per cent, as shown in Table 4 and Chart 2. This could reasonably be expected, but it may also indicate

that some docters were more suecessful than others with both V and Tm. If such is the case the suggestion of a necessary physiological relation between V and Tm must be taken with reserve. The effect of exercise upon them is utterly different, for vital capacity is not reduced at all, while Te, the length of small orifice blow begun 10 seconds after exercise, is less than half Tm, the length before exercise, showing that it is much better than vital capacity as a measure of shortness of breath.

TABLE 4.—CORRELATION COEFFICIENTS OF 309 FIRST-CLASS MALES.

Variables.	Correlation 100r per cent.	Prediction (100 $1-\sqrt{1-r^2}$ ), per cent.
Maximum length of blow: Before exercise (Tm, sec.) and 10 sec. after exercise (Te, sec.) . . . . .	51	14
Vital capacity (per cent V) and Tm . . . . .	49	13
Tm and T <sub>20</sub> . . . . .	42	9
V and Te . . . . .	32	5
T <sub>20</sub> and (Tm-S <sub>+</sub> ), 453 cases . . . . .	60	20

The failure of S<sub>+</sub> to correlate with Tm when T<sub>20</sub> did, was puzzling at first, for both T<sub>20</sub> and S<sub>+</sub> were believed to be measures of the tolerance of the circulation to increasing acidity. As the difference was thought to be that T<sub>20</sub> was standardized while S<sub>+</sub> was not, a rough correction for the length of blow was introduced by taking the difference (Tm-S<sub>+</sub>). This simple measure of irritability was found to be more closely related to T<sub>20</sub> than was Tm, as a glance at Charts 4 and 5 will show. Now probability theory would suggest less correlation between T<sub>20</sub> and (Tm-S<sub>+</sub>) than between T<sub>20</sub> and Tm, because there is practically no correlation of T<sub>20</sub> with S<sub>+</sub>, and combining these two quantities at random would be expected to vitiate the correlation. But Table 4 shows that by taking the function (Tm-S<sub>+</sub>) instead of S<sub>+</sub>, we have increased the correlation from 42 to 60 per cent. This is almost as high as the correlation between height and weight, so that we are justified in regarding both T<sub>20</sub> and (Tm-S<sub>+</sub>) as measures of irritability, and using one as a check on the other.

To compare these two measures of irritability quantitatively, they must be expressed in the same units. This can be done by taking the differences (T<sub>20</sub>-20) and (Tm-S<sub>+</sub>), but neither represents any geometric quantity on the systolic response curve. T<sub>20</sub> is the slope in arbitrary units of the line from the origin to the point representing a 20-mm. rise in systolic, so that the smaller T<sub>20</sub> the more rapid the systolic rise to this point. The ratio (20 Tm/S<sub>+</sub>) expresses in the same units the rapidity of the total systolic rise during the blow, and should normally be less than T<sub>20</sub>. If both are equal the origin and the points (T<sub>20</sub>, 20) and (Tm, S<sub>+</sub>) are all three in line.



The ratio ( $20 T_m/S_+$ ) is too involved for ordinary use. The borderline is fortunately  $T_m = S_+$ , and then the ratio reduces to 20. The borderline for  $T_{20}$  however, is 25, which again expresses the fact that the systolic pressure rises more rapidly after  $T_{20}$  has been reached. The scatter diagram (Chart 6) shows the relation of  $T_m-S_+$  to ( $20 T_m/S_+$ ), the circles representing first-class risks, the crosses clinical cases. The straight line ( $20 T_m/S_+ = 20 + (T_m-S_+)/2$ ) shows that the approximation is good enough for practical purposes near the abnormal borderline, in other words, that the difference is in direct proportion to the ratio, so that in practice it is sufficient to glance at  $S_+$  and see how it compares with  $T_m$ . If numerically greater it indicates irritability, and to check,  $T_{20}$  should be less than 25 seconds.

The number of cases in Table 4 is such that the probable error is about 3 per cent. It must be remembered that the coefficient of correlation expresses the percentage of the variations in the two responses which can be considered related, but the percentage of the variations in one response which can be predicted from those in the other is much smaller, as shown in the last column of the table. The coefficient ( $r = 0.51$ ) for example, proves that 51 per cent of the variations in  $T_m$  are proportional to those in  $T_e$ , but only the fraction ( $1-\sqrt{1-R^2}$ ) or 14 per cent can be predicted. To be able to predict even 50 per cent, the correlation would have to be at least 87 per cent, because of the confusion introduced by the random components of the variation. Thus, if weight is 70 per cent correlated with height among normals, only 30 per cent of the variations in weight can be predicted from height.

TABLE 5.—CORRELATION OF BLOOD PRESSURE RESPONSES.  
(Adult males, unimpaired or abnormal in arterial tension only.)

Variables.	No. cases.	Correlation, 100r, Per cent.	Prediction, $100(1-\sqrt{1-r^2})$ , Per cent.
Systolic (S) and:			
Diastolic (D), all values . . . . .	738	69	28
Diastolic D 80 and over . . . . .	335	68	27
Diastolic D under 80 . . . . .	403	40	8
Pulse pressure, (S-D) and:			
Diastolic (D), all values . . . . .	736	-15	1
Diastolic D 80 and over . . . . .	332	26	3
Diastolic D under 80 . . . . .	401	-13	1
Irritability ( $T_m-S_+$ ) and:			
Diastolic (D), all values . . . . .	738	-8	0
Diastolic D 80 and over . . . . .	335	-18	2
Diastolic D under 80 . . . . .	403	1	0
Pulse pressure (S-D), all values . . . . .	736	-10	0
Shortness of breath ( $T_m$ ), all values . . . . .	738	58	19
Shortness of breath (D 90 and over) . . . . .	85	47	12
Shortness of breath (D 60 to 89) . . . . .	634	56	17
Shortness of breath (D under 60) . . . . .	19	63	22

A more systematic study of the correlation of blood pressure responses is presented in Table 5. The high correlation of systolic

and diastolic pressure is, of course, familiar, but the coefficient is not, and so is computed as a basis for comparison. Apparently, the pulse pressure tends to rise above normal in both hyper- and hypotension, although the correlations are small. Irritability tends to increase slightly, that is ( $T_m - S_+$ ) to decrease, when the diastolic departs from normal, and also when the pulse pressure increases, but irritability accompanies shortness of breath much more frequently. The steady increase in this correlation from  $47 \pm 6$  per cent among the high diastolics, through  $56 \pm 2$  per cent for the normals, to  $63 \pm 9$  per cent among the low diastolics is suggestive, but the probable errors are too large to ascribe significance to this apparent trend.

**The Analysis of Overweight.** The Medico-Actuarial Investigation<sup>3</sup> showed a very wide spread among standard risks of the same sex, age and height, about the average weight for each class, which indicates that two individuals of the same sex, age and height may differ markedly in build and yet be normal. Therefore, the deviation from average weight may be partly due to a factor not necessarily related to impairment, and if this factor is properly corrected for, it is reasonable to expect a closer correlation with mortality than can be obtained from height and weight alone.

Vital capacity appears to be the most practicable anthropometric constant to use as a correction factor for body-build. It is more accurate than chest expansion or than the chest-waist difference. Moreover, in itself it is an important physiologic constant, for it indicates the alveolar surface available for oxygen exchange. Its reduction, therefore, must be considered an impairment, although the safety factor is large, and moderate limitation in vital capacity does not in itself lead to shortness of breath.

Now vital capacity is about as closely correlated with height as weight is, so it is reasonable to expect individuals with vital capacities above normal for a given height to be somewhat overweight because of build alone, and not because of excess fat. In other words, weight should normally increase with vital capacity at constant height, and such positive correlation would not indicate impairment. Overweight as an impairment should be negatively correlated with vital capacity.

Mortality is found to increase also among underweights at the younger ages. Vital capacity should, therefore, be below normal among impaired underweights, that is, it should be positively correlated with weight. For example, in pulmonary tuberculosis the weight and vital capacity go down together as the disease advances.

The measure of shortness of breath ( $T_m$ ), however, would not be expected to vary in the same way as a function of weight, for it is practically independent of height. A combination of overweight with reduced  $T_m$  and  $V$ , therefore, is cumulative evidence of impairment on three counts at once, while moderate overweight with

normal  $T_m$  and large  $V$  indicates merely an individual of large build. Hence, such a class of overweights may be regarded as less impaired than others with the same excess weight.

Our data are as yet too meager to test these ideas with any conclusiveness, but a preliminary study of 700 cases already shows that the general direction of the results is just as expected except for standard underweights. Only 14 cases were rated for overweight alone; 3 of these showed both irritability and shortness of breath, 1 shortness of breath, 2 borderline shortness of breath, and 8 gave normal flarimeter reports. All showed vital capacity normal or above. The percentage of abnormal reports is nearly twice, and that of inconsistent about one-third the average percentage for all rated cases. Thus, the test may prove quite useful in estimating the burden of overweight.

The only correction that has been made in vital capacity is to add 1 per cent per year over age 40 to the percentage of normal from Myers' tables by sex and height, "but this correction is evidently too much. One-half per cent per year over 40 would probably be nearer the average decrease with age."<sup>4</sup>

**Progressive Stages of Impairment.** It is already fairly evident that most of the responses in flarimeter tests increase with increase in function, and that reduction spells impairment. No one can believe that additional lung capacity ( $V$ ) is any handicap, and the lengths of blow ( $T_m$ ,  $T_e$ , and  $T_r$ ) before and after exercise cannot decrease very much before one is conscious of shortness of breath. The irritability indexes ( $T_{20}$  and  $T_m - S_+$ ), also show no tendency to increase, but always to decrease as impairment proceeds, at least in typical heart cases, until the disease is advanced. The older measures, pulse rate and blood pressure, on the other hand, present optimum values above and below which the interpretation is less favorable.

The borderlines between normal and abnormal, too, are approximately established. It will take a long time, however, for the precise meaning of the flarimeter report to be known, for the possible varieties are innumerable. Suppose each response were limited to two values, "good" or "bad." Even then there would be over 33 million different reports possible, by permuting the 25 different responses on each report. Eleven of these, however, may be regarded as checks, leaving 14 which are significantly different. These 14 would still furnish over 16,000 varieties of reports. But each response can have many more than two values, indeed, it is only a point on a continuous quantitative scale. Failure to appreciate these complexities is perhaps responsible for the shallow enthusiasm and impatient skepticism sometimes accorded such tests.

The most casual inspection of flarimeter reports, however, is sufficient to show that the responses are not random. They possess a close relationship which reduces enormously the varieties encoun-

tered. Apparently the first sign of circulatory trouble is the irritability shown by a shortened  $T_{20}$  and an exaggerated systolic rise ( $S_+$  larger than  $T_m$ ). It is not certain which of these signs is the more sensitive, probably they represent much the same thing. Sometimes this is preceded or accompanied by emotional hypertension.

The next stage is shortness of breath, which should appear first as a reduction in  $T_e$ , then in  $T_r$ , and finally in  $T_m$ , although differences in performance may easily confuse the issue. Irritability should be more marked at this stage, but the vital capacity should be normal.

As the cardiac impairment advances, even the vital capacity begins to be reduced, and finally the heart muscle fails to produce sufficient systolic response. Advanced cases, however, perform so poorly that one never feels sure that a short blow with insufficient systolic response represents any approach to an individual's possible limit.

Most of the heart cases fall into place in this scheme which appears rational on physiologic grounds. There are not enough cases yet, however, to justify systematic presentation. The most consistently abnormal tests were met in hypertension (57 per cent of 37 rejected cases), particularly when complicating a heart murmur (63 per cent of 16 cases). On the other hand, only 5 per cent of 19 cases called "functional murmur" by the examiner, but nevertheless rated, gave consistently abnormal flarimeter reports, while normal reports were obtained in 48 per cent of 21 cases rejected with heart murmurs as against 12 per cent of 16 cases with both murmurs and hypertension.

Apparently, murmurs, hypertrophy, abnormal pulse or blood pressure, toxic goiter, tuberculosis and overweight are the impairments with which the typical picture we have outlined is most consistent. Cases with glycosuria or albuminuria, however, seem to present quite a different type of flarimeter test. Thus, in 43 cases rated or rejected for sugar or albumin in the urine, only 21 per cent of 14 glycosurias showed irritability and only 3 per cent of 29 albuminurias; 21 per cent of the former showed consistent shortness of breath, 14 per cent of the latter. Only one each showed both irritability and shortness of breath, 3 and 7 per cent, respectively. The outstanding characteristic seemed to be a very marked reduction in  $T_r$  relative to  $T_m$ . We suspect that such cases may often show responses different from the cardiac type, perhaps due to changes in the acid-base balance of the blood and tissues.

We do not yet begin to know the functional pathology of the respiratory center, the tolerance of which to acidity largely determines the length of blow. In some conditions, such as uncomplicated chronic pulmonary emphysema, an exaggerated tolerance to  $CO_2$  is developed,<sup>5</sup> but in uncomplicated cardiac impairments, appar-

ently, the burden is borne by the myocardium, and a tolerance to acidity does not develop or may even be reduced. Thus, we cannot interpret fully, as yet, an insufficient systolic response with no shortness of breath, which we have encountered a few times, apparently, in both normal and abnormal cases.

**Errors of Performance.** If no steps are available the exercise is not standard, that is, the amount of work done is neither measurable nor under control. Nevertheless, we are not utterly helpless, for *Te*, the length of blow immediately after exercise can be used as a gauge of the oxygen debt incurred. If this is normal (about 20 seconds), the exercise may be considered approximately standard, although it is evident that substandard exercise may produce the normal *Te* in a substandard case. Moreover, a subnormal *Te* may indicate merely that the bending movements were made with more than standard vigor. Such doubts do not occur with the standard step exercise, in which the rate and amount of work done are accurately controlled, so that for comparative purposes and doubtful cases the exercise test should always be standard.

The examiner must not allow excessive overbreathing either before or between small orifice blows, for this washes carbon dioxide out of the blood and enables the subject to blow longer. A certain amount of overbreathing, of course, is to be expected. It is the conscious effort to increase his score that must be guarded against, or taken into consideration in the interpretation.

There is one other trick which may slip by unperceived, while the examiner is absorbed in following the systolic rise. This is "breath-snatching." Whenever attempted, the water in the manometer falls abruptly, as indeed does the systolic pressure, so that it is immediately evident, and the test should be stopped and begun again. It is rarely attempted if the doctor stresses the necessity of holding the manometer level steady.

The usual error of performance, however, is the failure of the individual to give a blow approaching his physiologic limit. In such cases the systolic pressure often fails to rise even 20 mm., and such tests are of little value. Without real coöperation no functional test requiring conscious effort can possibly succeed. Fortunately, most subjects enjoy the test and do their best. Others, who mean well but are unfamiliar with the subjective sensations of air hunger, can be encouraged to put forth a real effort. Their second and third blows in Tests II and III are usually quite successful.

When the doctor himself makes the test, the allowances to be made for errors of performance are fairly obvious at the time of the test, and should be recorded immediately in the space for remarks, as a part of the original data. But suppose one attempts to interpret a test made by another, the values recorded are often

the only data available. To illustrate how we would handle Test III, the series of responses shown in Table 6 are interpreted as single blows, although in an actual case all the evidence must be considered.

TABLE 6.—INTERPRETATION OF TEST III.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)
Systolic . . . . .	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120
T <sub>20</sub> (sec.) . . . . .	40	35	20	20	40	30	25	30	40	20	20	20	30	..	15
Maximum systolic . . . . .	150	160	160	180	180	150	160	160	160	145	160	145	140	130	160
T <sub>20</sub> (sec.) . . . . .	60	50	50	50	50	40	40	35	35	35	30	30	30	25	25
S <sub>+</sub> (mm.) . . . . .	30	40	40	60	60	30	40	40	40	25	40	25	20	10	40
Classification:															
T <sub>m</sub> . . . . .	N	N	N	N	N	B	B	A	A	A	A	A	A	A	A
T <sub>m</sub> -S <sub>+</sub> . . . . .	N	N	N	A	A	N	B	A	A	N	A	N	N	N	A
T <sub>20</sub> . . . . .	N	N	A	A	N	N	N	N	N	A	A	A	N	..	A

N = normal; B = borderline; A = abnormal.

#### Interpretation.

- (1) Exceptionally good (examiner may have missed maximum systolic).
- (2) Perfectly normal (probably correct).
- (3) Probably normal (T<sub>20</sub> may be an error).
- (4) Consistently irritable (probably correct).
- (5) Blew his best, but slightly under par (T<sub>20</sub> looks a bit too long).
- (6) Not his best, no abnormality shown.
- (7) Irritable and short of breath.
- (8) A suspicious test, repeat (may have missed T<sub>20</sub>).
- (9) Irritable and short of breath (T<sub>20</sub> a mistake).
- (10) Irritable and short of breath perhaps (probably missed peak in systolic).
- (11) Consistently irritable and short of breath.
- (12) Probably irritable and short of breath (missed systolic peak or else T<sub>20</sub>).
- (13) Consistent perfunctory performance (values check).
- (14) Either lazy or advanced ease of myocardial degeneration.
- (15) Advanced irritability and shortness of breath (toxic goiter?).

The data in Test V are compared in the same spirit, trying to visualize the performance at each step and giving the subject the benefit of the doubt wherever possible, for one good response is usually more significant than two bad ones. Indeed, if we assume correct observations, we must be liberal with the systolic responses, for emotional disturbance may easily cause momentary fluctuations which cannot be taken too seriously. When irritability appears in more than three out of the six systolic responses in Test III, however, it cannot be considered lightly, especially if the T<sub>m</sub>'s, T<sub>e</sub> and T<sub>r</sub> are not consistently good. If all three T<sub>m</sub>'s are bad, both T<sub>e</sub> and T<sub>r</sub> should also be bad, of course, but if three of the five are good, the other two may be due to faulty performance. Every effort of persuasion should be made to get the longest possible final blow (T<sub>r</sub>). It is a great advantage to have the systolic responses during this blow also, as we do in our latest technique, for this often settles the question. When T<sub>r</sub> is a bit short, a normal T'<sub>20</sub> and (T<sub>r</sub>-S'<sub>+</sub>)

are reassuring, especially when Test III is normal, and when  $Tr$  is exceptionally long, these values help in revising our estimate of Test III. On the other hand, if  $Te$  is poor, and the pulse and blood pressure returns delayed, and both  $T'_{20}$  and  $(Tr-S'_+)$  are short, a subnormal  $Tr$  cannot reasonably be assumed to be merely an accident, as some patients will claim.

W. W. Herrick<sup>6</sup> considers that the most satisfactory exercise test for all types of cases is the performance of enough work to bring about moderate dyspnea. For ambulatory patients, however, the better standardized exercise of Master and Oppenheimer which we have adopted is quite practical, and the length of flarimeter blow immediately thereafter measures quantitatively the dyspnea produced. It is, therefore, much more satisfactory for comparative purposes.

In Fig. 1, Test V shows three responses to exercise: (1) Shortening of the blow immediately after; (2) extent of return of pulse toward its original rate, at the end of the second minute; (3) length of blow 2 minutes after exercise (allowing for the interruption in breathing during the previous blow). As now standardized, however, a further improvement in the test has been made by leaving the cuff and stethoscope attached to the arm (disconnecting the tubes) during the standard step exercise and then observing the pulse, systolic and diastolic returns and the systolic response during the final blow. This increases the number of observations to *eight*, without taking any more time, and so provides a very complete picture of the response to exercise. Further details will be gladly supplied to those interested.

**Summary.** Normal values and abnormal borderlines for all flarimeter responses are determined empirically.

By analysis of the first 1500 cases, a basis is established for interpretation.

Individuals with vital capacities above normal for a given height should appear somewhat overweight because of build alone. Vital capacity is the best available factor for correcting overweight by height, age and sex.

Cardiac impairments seem to show the following progressive changes:

1. *Irritability*, i. e., shortened  $T_{20}$  and exaggerated systolic rise; often accompanied by emotional hypertension.

2. *Shortness of breath*, the length of flarimeter blow, first reduced 10 seconds after standard exercise, then 2 minutes after also, and finally both before and after exercise. Irritability should be more marked at this stage, but the vital capacity should be normal.

3. Further shortness of breath, but less irritability.

4. Even the vital capacity reduced.

5. Insufficient systolic response.

Atypical flarimeter tests, showing CO<sub>2</sub> tolerance, but great shortening of breath after exercise, seem to characterize the 43 uncomplicated urinary cases so far accumulated. Complicated cardiorenal cases give too great a variety to classify the few tests as yet available.

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## THE EFFECT OF BLOOD TRANSFUSIONS ON BONE-MARROW ACTIVITY AS INDICATED BY THE RETICULOCYTE COUNT.

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THE use of blood transfusions as a therapeutic agent is finding an ever-widening field in practically all branches of medicine. It is, therefore, of considerable interest to determine how transfusions act and what effect they have on the blood-forming organs. It is obvious that the immediate benefit derived from a transfusion is the result of the purely mechanical addition of a certain volume of blood to the circulation. Many transfusions are given for this reason alone, as in cases of hemorrhage. However, it is also a common practice in hospitals to transfuse patients who are depleted by disease, but who have not actually had any direct loss of blood. Transfusions in cases of this character are usually small in amount, but frequently repeated. Clinicians speak of these as stimulating transfusions, and the inference is that they not only have an immediate effect in supplying blood, but also have a subsequent stimulating action on the hematopoietic system. The purpose of this work is to study the effect of a number of unselected routine transfusions on the bone marrow. The percentage of reticulocytes in the peripheral blood is used to estimate bone-marrow activity.

Hess<sup>1</sup> and Itami,<sup>2</sup> who were the first to describe the changes in



the bone marrow after transfusion, used the histologic changes in the bone marrow of rabbits as criteria of the effect of the transfusions. Their results were not conclusive, since there is considerable normal variation in the red marrow of normal rabbits.

Robertson,<sup>3</sup> and subsequently Krumbhaar and Chanutin,<sup>4</sup> studied the effects of experimental plethora on the bone marrow of rabbits and dogs, using the percentage of reticulocytes as an index of bone-marrow activity. There was no notable change in the percentage of reticulocytes until the animals had been given several transfusions. When the plethora became well defined the number of reticulocytes in the blood began to diminish.

Vogel and McCurdy<sup>5</sup> studied the reticulocytes in cases of pernicious anemia after transfusion. They found, in several cases where large amounts of blood had been given, a marked drop in the reticulocytes. These patients did badly. Minot and Lee<sup>6</sup> observed a similar effect after large transfusions in pernicious anemia. This severe depression and poor clinical result has been explained as follows: In severe cases of pernicious anemia the marrow is very nearly exhausted. The stimulus of the anemia with its oxygen lack is just enough to keep it functioning. A sudden lowering of this stimulus is produced by a large transfusion and the activity of the marrow is markedly depressed. It follows, therefore, that in cases of pernicious anemia with feebly reacting bone marrow, as indicated by the reticulocyte count, small transfusions are preferable to large ones.

Our series consists of 25 cases and 6 controls. These cases vary in the diseased condition present and in the amounts of blood transfused. They have been studied with particular reference to the reticulocyte response after transfusion. We would disclaim all responsibility for the amounts of blood transfused, since these amounts were specifically ordered by the clinicians.

**Technique.** Blood counts, including reticulocyte percentage, were done before transfusing the patient and at varying intervals afterward for 2 weeks. This time limit was considered sufficient for any marked changes to occur. Similar counts were done on the donors so as to check up on the number of reticulocytes in the transfused blood. The counts were done in the usual way (hemoglobin by the Sahli method, red counts with carefully standardized pipettes, and reticulocytes on cover-slip preparations stained with brilliant cresyl blue (Grübler) and counterstained by the Jenner-Giemsa method). In estimating the percentage of reticulocytes 1000 red cells were counted, using an oil-immersion objective with a special grating ocular. The donors had red blood counts averaging from 4,000,000 to 5,000,000, with reticulocytes between 0.5 and 1 per cent. The transfusions were done by the Lindemann multiple syringe method.

## CASE REPORTS.

	Hb., per cent.	R. B. C. millions per c.mm.	Retic., per cent.	Trans- fusion, cc.	Diagnosis and remarks.
Case 1:					
May 19 . .	25	0.75	7.0		Pernicious anemia
May 20 . .	...	...	...	600	
May 21 . .	32	0.8	3.9		Liver treatment
May 23 . .	35	2.0	4.0		
May 25 . .	40	2.0	4.5		Female, aged 39 years
May 28 . .	45	2.2	4.8		
May 29 . .	...	...	...	400	
May 30 . .	59	2.9	3.9		
May 31 . .	...	...	...	600	
June 2 . .	70	3.9	2.0		
June 3 . .	...	...	...	600	
June 4 . .	80	4.0	0.6		
June 5 . .	...	...	...	500	
June 6 . .	90	4.4	0.4		
Case 2:					
April 10 . .	41	2.1	2.0		Anemia primary(?)
April 11 . .	...	...	...	300	
April 12 . .	48	2.6	1.6		Female, aged 51 years
April 14 . .	45	2.4	1.5		
April 16 . .	49	2.5	1.6		
April 20 . .	50	2.8	1.3		
April 22 . .	53	2.9	1.7		
April 25 . .	55	3.1	1.5		
Case 3:					
April 8 . .	59	4.0	4.0		Multiple myeloma
April 9 . .	...	...	...	250	
April 10 . .	65	4.2	2.0		Male, aged 25 years
April 12 . .	63	4.0	2.0		
April 15 . .	60	3.8	2.5		Patient left hospital
April 19 . .	57	3.6	3.0		
April 25 . .	50	3.2	4.0		
April 26 . .	...	...	...	250	
April 27 . .	54	3.0	3.3		
April 29 . .	50	2.8	3.5		
May 1 . .	...	...	...	250	
May 2 . .	64	3.1	1.8		
Case 4:					
October 29	43	2.6	1.6	300	Bleeding gastric ulcer
October 30	50	3.2	2.0		
November 3	62	3.5	2.0		Male, aged 35 years
November 6	56	3.0	1.0		
November 12	62	3.8	0.4		
Case 5:					
April 17 . .	70	4.1	0.6	300	Uterine fibromyomata
April 18 . .	78	4.5	0.5		
April 19 . .	...	...	...	250	Female, aged 31 years
April 20 . .	84	5.0	0.2		
April 23 . .	85	4.6	0.4		Hysterectomy
April 27 . .	83	4.3	0.7		
May 1 . .	85	4.5	0.5		

	Hb., per cent.	R. B. C., millions per c.mm.	Retic., per cent.	Trans- fusion, cc.	Diagnosis and remarks.
Case 6:					
May 17 . . .	60	3.1	2.1	200	Acute mastoiditis
May 19 . . .	68	3.9	2.6		
May 21 . . .	70	4.1	2.0		Female, aged 4 years
May 22 . . .	...	...	...	200	Operation
May 23 . . .	77	4.9	2.2		
May 27 . . .	75	4.4	1.8		
May 30 . . .	75	4.3	1.6		
Case 7:					
October 9 . .	35	1.8	11.0	350	Primary anemia
October 10 . .	45	2.1	9.5		
October 13 . .	60	2.2	5.0		Female, aged 63 years
October 14 . .	...	...	...	350	Liver treatment
October 15 . .	61	2.3	1.0		
October 17 . .	54	2.4	0.4		
October 19 . .	55	2.2	0.1		
October 23 . .	59	2.7	0.1		
Case 8:					
October 11 . .	53	3.2	0.8	100	Pneumonia
October 13 . .	66	4.2	0.8		
October 15 . .	60	4.0	1.1		Male, aged 10 months
October 17 . .	65	4.3	0.8		
October 20 . .	70	4.5	0.2		
October 24 . .	72	4.4	0.4		
Case 9:					
October 18 . .	65	3.5	0.8	80	Pneumonia
October 20 . .	74	4.0	1.2		
October 22 . .	72	4.2	0.6		Male, aged 6 months
October 24 . .	76	4.3	0.8		
October 28 . .	78	4.5	0.8		
November 1 . .	75	4.2	0.6		
Case 10:					
October 22 . .	65	3.8	0.2	180	Pneumonia
October 23 . .	66	3.9	0.4		
October 25 . .	65	4.0	0.8		Male, aged 2 years
October 27 . .	66	4.1	0.5		
November 1 . .	62	3.2	1.5		
November 6 . .	63	3.4	1.2		
Case 11:					
April 20 . . .	63	3.7	2.0		Tuberculosis of kidney
April 21 . . .	...	...	...	300	
April 22 . . .	65	3.8	2.5		Female, aged 23 years
April 23 . . .	...	...	...	300	
April 24 . . .	66	4.3	2.0		Nephrectomy
April 28 . . .	65	4.0	1.8		
May 1 . . .	65	4.2	2.0		
May 5 . . .	67	4.1	2.5		
May 14 . . .	67	4.3	2.1		
Case 12:					
October 31 . .	28	1.4	0.6	350	Acute myeloblastic leu-
November 1 . .	45	2.0	0.2		kemia
November 3 . .	35	1.8	0.1		Male, aged 13 years
November 7 . .	25	1.2	0.1		Died; autopsy, diagnosis confirmed

	Hb., per cent.	R. B. C., millions per c.mm.	Retie., per cent.	Trans- fusion, cc.	Diagnosis and remarks.
Case 13:					
October 29	45	2.3	0.8	400	Carcinoma of lung
October 30	52	2.8	1.0		
November 3	48	2.7	0.6		Male, aged 58 years
November 6	48	3.1	0.8		
November 11	49	2.8	0.8		
November 13	48	3.2	0.8		
Case 14:					
November 4	65	3.6	0.2	500	Tuberculosis of ovaries
November 5	68	4.1	0.2		
November 7	63	3.2	0.4		Female, aged 28 years
November 11	65	3.5	0.8		
November 15	63	3.6	0.6		Operation
November 19	56	3.0	0.4		
Case 15:					
November 7	65	3.7	0.9	350	Sepsis(?)
November 10	69	3.9	0.8	350	Male, aged 38 years
November 11	77	4.3	0.1		Died; autopsy, miliary tuberculosis
Case 16:					
November 4	74	6.0	0.8	150	Malnutrition; marasmus
November 5	110	7.2	1.0		dehydration
November 7	105	8.2	0.2		Male, aged 9 months
November 8	...	...	...	150	
November 10	120	9.6	0.2		Died
Case 17:					
December 5	74	4.7	1.0	400	Thrombophlebitis of leg
December 8	63	3.9	1.0		
December 10	69	4.0	0.4		Male, aged 50 years
December 11	68	3.7	0.4		
December 15	69	4.2	1.0		
December 17	70	3.9	0.6		
December 19	70	3.8	1.0		
Case 18					
December 5	46	3.9	0.8	150	Acute mastoiditis
December 8	62	4.5	0.6		
December 10	59	4.3	0.6		Male, aged 1½ years
December 12	63	4.6	0.8		
December 16	67	4.8	0.6		Operation
December 18	65	4.4	0.8		
December 20	67	4.5	0.4		
Case 19:					
December 5	71	4.3	2.0	80	Furunculosis, malnutrition
December 8	93	6.2	1.6		
December 10	74	4.2	0.8		Male, aged 4 months
December 12	70	4.3	0.4		
December 16	75	4.5	0.2		
December 18	72	4.4	0.4		
December 20	73	4.5	0.2		
Case 20:					
December 12	30	2.6	3.0	500	Carcinoma of rectum, inoperable
December 15	39	3.0	2.2		
December 17	37	3.2	0.5		
December 19	38	2.7	0.2		Male, aged 57 years
December 22	35	2.5	0.1		
December 24	33	2.3	0.1		
December 27	34	2.2	0.1		

	Hb., per cent.	R. B. C., millions per c.mm.	Retic., per cent.	Trans- fusion, cc.	Diagnosis and remarks.
Case 21:					
December 13	75	4.2	1.0	60	Malnutrition, pneumonia
December 15	80	4.3	0.4		
December 17	81	4.3	0.2		Male, aged 5 months
December 19	82	4.6	0.2		
December 20	...	...	...	80	
December 22	109	6.8	0.1	80	
December 23	110	6.5	0.1		
December 24	98	5.7	0.2		
December 26	123	6.5	0.1		
Case 22:					
December 8	30	1.4	1.2	350	Subleukemic myeloid leukemia
December 9	35	1.8	1.2		
December 11	36	2.0	1.2		
December 13	35	2.0	1.0		Male, aged 45 years
December 16	34	1.7	0.2		
December 18	35	2.1	0.4		
December 19	...	...	...	360	
December 20	44	2.9	0.2		
December 23	37	1.8	0.1		
December 26	35	1.7	0.1		
Case 23:					
December 23	36	2.2	0.6	300	Bleeding from cervix, possible carcinoma of cervix, chronic nephritis
December 24	38	2.9	0.2		
December 27	40	2.7	0.3		
December 30	36	2.0	0.2		
January 2	40	2.2	0.2		Female, aged 39 years
January 6	40	2.4	0.3		
Case 24:					
December 9	53	3.0	0.4	500	Pneumonia
December 10	55	3.2	0.4		
December 12	59	3.5	0.3		Female, aged 2 years
December 15	59	3.4	0.6		
December 17	65	3.9	0.2		
December 19	68	3.9	0.1		
December 22	71	4.0	0.2		
Case 25:					
December 22	30	1.5	0.6	250	An aplastic anemia
December 23	33	1.6	0.4		
December 26	36	1.9	0.6		Male, aged 12 years
December 29	29	1.4	0.6		
December 31	30	1.5	0.7		Liver treatment begun
January 3	31	1.5	1.0	250	January 5
January 5	42	2.4	1.2		
January 10	42	2.4	0.6		
January 13	42	2.5	0.4		
Control Case 1:					
December 29	51	3.2	1.0		Carcinoma of kidney
December 31	55	3.5	3.4		
January 3	62	4.1	4.0		Male, aged 37 years
January 7	61	4.0	0.8		
January 10	56	3.6	2.1		
January 12	58	4.1	1.0		

	Hb., per cent.	R. B. C., millions per c.mm.	Retic., per cent.	Diagnosis and remarks.
Control Case 2:				
December 29 . . . .	77	4.1	1.2	Chronic infectious arthri- tis
December 31 . . . .	74	3.9	1.4	
January 3 . . . .	79	4.3	0.8	Male, aged 31 years
January 7 . . . .	75	4.0	0.2	
January 10 . . . .	74	4.1	0.4	
January 12 . . . .	76	4.2	0.7	
Control Case 3:				
December 29 . . . .	60	3.5	0.1	Carcinoma of lung
December 31 . . . .	63	3.8	0.1	
January 3 . . . .	67	3.9	0.1	Male, aged 41 years
January 7 . . . .	64	3.6	0.2	
January 10 . . . .	59	3.5	0.1	
January 13 . . . .	62	3.3	0.1	
Control Case 4:				
December 30 . . . .	82	4.1	0.1	Acute appendicitis
January 2 . . . .	84	4.4	1.4	
January 6 . . . .	89	4.5	0.8	Female, aged 17 years
January 8 . . . .	92	4.6	0.1	
January 9 . . . .	89	4.5	0.1	Operation
January 12 . . . .	90	4.3	0.1	
Control Case 5:				
December 30 . . . .	77	3.9	1.0	Pneumonia
January 2 . . . .	80	4.0	1.2	
January 6 . . . .	80	4.1	0.2	Female, aged 30 years
January 8 . . . .	82	4.4	0.6	
January 9 . . . .	85	4.3	0.2	
January 13 . . . .	87	4.5	0.1	
Control Case 6:				
December 30 . . . .	67	4.1	1.2	Chronic ulcer of stomach
January 2 . . . .	65	3.7	0.4	
January 6 . . . .	73	4.0	1.0	Male, aged 60 years
January 8 . . . .	70	3.5	1.4	
January 9 . . . .	67	3.8	0.5	
January 13 . . . .	71	4.1	1.0	

**Discussion.** From a study of the data presented, it is evident that large transfusions are followed by a drop in the reticulocyte percentage. Small transfusions are not followed by any definite rise in reticulocytes, which would suggest that their effect is similar to but less in degree than that of the large transfusions. A slight rise in reticulocytes, such as an increase of 0.5 to 1 per cent after transfusion means nothing, as the control cases show that this small variation in the reticulocyte percentage can occur from day to day in secondary anemia without transfusion, and moreover it is probably within the limit of error of this method.

As to the meaning of these findings, there are several possibilities. Transfusions may have some effect in improving maturation in the bone marrow, and the decrease of reticulocytes when associated with an increase in red blood cell count might thus be due to more mature red blood cells being formed. Then again, as Robertson<sup>3</sup> and Krumbhaar and Chanutin<sup>4</sup> have shown, the decrease in the

percentage of reticulocytes may reflect the lessened demand on the bone marrow because of the increased number of red cells temporarily available in the blood stream after transfusion. The latter interpretation, which seems the more plausible, would mean that transfusions are followed by a depression of bone-marrow activity.

In cases in which the bone marrow is exhausted, as in pernicious anemia, transfusions should be used with discretion and it is advisable for the clinician to consult with the transfusionist with regard to the amount of blood to be given.

**Summary and Conclusions.** 1. A series of 25 routine cases and 6 controls are presented in which the effects of blood transfusions on bone-marrow activity were studied. The percentage of reticulocytes in the peripheral blood was used as an index of bone-marrow activity.

2. An increase in the red blood cell count following transfusions is associated with a decrease in the percentage of reticulocytes.

3. This finding can be interpreted as meaning either (a) that transfusions aid in improving maturation of red cells in the bone marrow, or (b) (more likely) that transfusions by lessening the stimulus are followed by a depression of bone-marrow activity.

NOTE.—Grateful acknowledgment is due Dr. G. L. Rohdenburg, Director of the Laboratory, for his criticism of the manuscript, and Miss D. Green for technical assistance.

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## PRIMARY HYPOCHROMIC ANEMIA (ERYTHRO-NORMOBLASTIC ANEMIA).

### A NEW TYPE OF IDIOPATHIC ANEMIA.

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THE observation recently of a group of patients with marked anemia whose clinical picture resembled in many respects pernicious anemia, but whose blood picture was that of a marked "secondary" anemia, resulted in an attempt at formulation of a new clinical entity, especially since treatment with iron rather than with liver

was effective in producing a remission. This condition I have called "primary hypochromic anemia."

With respect to nomenclature, the purely descriptive, almost naïve name "pernicious anemia" has been made archaic since the advent of liver therapy. As Schilling<sup>1</sup> has pointed out, the disease might more properly be called "megaloblastic hyperchromic anemia"—"megaloblastic" referring to the bone-marrow pathology which is characterized by the overproduction of megaloblasts (and macrocytes)—"hyperchromic" referring to the high color index, the individual red blood cell being filled with at least its normal complement of hemoglobin. This type of anemia has also been called "primary" because it is an anemia apparently arising *de novo* and comprising a distinct disease entity. Another of the "primary" types of anemias is "idiopathic" aplastic anemia which also is "hyperchromic" in that it exhibits a color index of unity or above. The anemias secondary to various known causes, such as hemorrhage, infection, carcinoma and toxic conditions, however, are associated with a color index of less than unity—and are thus "hypochromic." Thus the concept has gradually developed that blood-pictures of anemia with hyperchromia and a color index of one or over are idiopathic and those showing hypochromia and a color index less than one are "secondary." That there are cases, however, in which hypochromia is present and yet the anemia is "primary" is not as yet generally recognized, so that even when no cause for the anemia can be found after diligent search, there is still the feeling that the anemia is not "primary" but secondary to some unknown cause.

In the last 2 years, several patients with a severe anemia for which no cause could be found, have been observed. This anemia was subject to spontaneous remissions and relapses, was associated with such symptoms as sore tongue and paresthesias, and showed objectively an atrophied tongue and (usually) achlorhydria. Hematologically, there was a "secondary" type of blood picture: *i. e.*, a low color index, hypochromia, and a diminished average red blood cell diameter. The anemia did not improve with liver therapy, but there was striking response to large doses of iron. In other words, it was felt that these patients were suffering from a form of "primary" anemia; and, since this anemia was associated with hypochromia rather than with the more common hyperchromia, it was called primary hypochromic anemia. In the course of the study of these patients, various relationships to Addisonian or pernicious anemia suggested themselves, resulting in the concept that there might be two types of pernicious anemia—the megaloblastic, associated with macrocytosis and hyperchromia, and the erythroblastic, associated with microcytosis and hypochromia. It is the purpose of this paper to bring out these possible relationships and to attempt to awaken interest in a hitherto but little recognized clinical entity.



The treatises on diseases of the blood make no mention of this form of anemia as an entity. Within the past year, however, there have been several reports of a similar type of hypochromic anemia under various names according to the author reporting it. Thus Kaznelson, Reiman; and Weiner<sup>2</sup> describe achylic chloranemia ("achylische chloranämie"), a term also used by Schulten.<sup>3</sup> Mills<sup>4</sup> calls it idiopathic hypochromic anemia. Altschuler<sup>5</sup> speaks of chronic hypochromic anemia ("anémie hypochrome chronique"). Faber<sup>6</sup> uses the terms simple anemia, simple hypochromic anemia, simple achylic anemia, and microcytic anemia. Wahlberg<sup>7</sup> mentions "simple anemias" associated with achylia. Castle<sup>8</sup> in all probability refers to this group of cases when he speaks of "chronic chlorosis." Mettier, Minot and Townsend<sup>9</sup> in their discussion of the treatment of the anemia of scurvy, refer to "anemias of ill defined origin particularly occurring in women and often associated with gastric anacidity." Witts<sup>10</sup> and Waugh<sup>11</sup> in recent articles, describe hypochromic anemias associated with achylia. It is thus seen that interest in this type of anemia is gradually increasing.

**Report of Cases.**—Our interest in this unusual type of anemia was stimulated by the case of Helen H. (Case 1 of the present series). After this case was studied, its relationship to other similar cases immediately suggested itself. These cases are the subject of the present report.

**CASE 1.**—B. I. H., No. 7142. Helen H., a married housewife, aged 44 years, a native of Canada who had lived in New England for 4 years, was admitted to the Beth Israel Hospital of Boston on July 1, 1930, complaining of pallor and dyspnea on slight exertion. Family history was unimportant. Past history disclosed the following diseases: questionable rheumatic fever annually from the ages of 11 to 14; typhoid fever at 16; "malaria" about 10 years ago lasting for about a month, never recurring; an "inflamed right ovary" 9 years ago culminating in an operation for appendectomy and right oöphorectomy; influenza 6 years ago; and knowledge of a nodule in the thyroid gland for 5 years. Catamenia which began at the age of 12, had always been regular, lasting for 4 to 5 days. Ten years previously she weighed 160 pounds, but had gradually lost weight during the past 5 years so that on admission she weighed 121 pounds. Repeated questioning disclosed that the present illness began in reality about 5 years before admission. At that time, she became markedly pale, weak, dyspneic on the slightest exertion, had 3 to 5 loose movements daily, and lost 30 to 40 pounds in weight. She was at that time in St. John, New Brunswick, where she consulted a doctor who told her she was "anemic" and gave her "iron pills" of which she used 100. Her color and strength gradually returned and she gained 20 pounds in weight. However, 4 years previously she again developed the above symptoms, again took the same iron pills, and was again relieved. She then felt well until 2 years before admission when the identical symptoms of weakness, pallor, loss of weight, and diarrhea recurred. She had by now lost her iron prescription and did not consult a doctor. A year and a half ago, she developed increased menstrual flow and at times would flow between periods. The symptoms were at their worst in December, 1929. At this time, her tongue became markedly sore so that she was unable to eat oranges or any other "acid" fruits or vegetables; she consulted a doctor about this and was given a mouth wash with but little relief. After this, she developed numbness and tingling

of the fingers and toes. Pallor gradually grew worse; she again had 3 to 5 loose bowel movements daily; she could hardly drag herself about and was dyspneic even on walking across the floor. She finally came to the Boston Dispensary in June, 1930, and was referred to the Beth Israel Hospital for study. At no time had she taken any drugs other than those mentioned above. Appetite was extremely poor but she ate meat, green vegetables and fruits in moderate amounts. Her ordinary dietary was: breakfast—toasted white bread, cereal, coffee or tea; luncheon—bacon, egg, potato, tea or coffee; supper—stew (vegetables, meat), green vegetable salad, pie. She had 2 oranges and 2 glasses of milk daily.

*Physical examination* on admission showed a well-built but very thin woman with extreme pallor. She weighed 121 pounds. The skin color seemed at first glance yellowish, but this was found to be due to the extreme pallor of the tissues rather than to icterus. The scleræ showed no icterus whatever. The patient's eyes were brown in color, as was the hair. The tongue was smooth, atrophied, and without coat; there was some redness at the edges. The buccal mucosæ were very pale. A firm nodule, the size of a walnut, was present in the right lobe of the thyroid gland. There was a soft systolic murmur over the precordium; otherwise the heart showed nothing abnormal. The liver edge was felt 1 to 2 fingers' breadth below the right costal margin; the spleen was not felt except once by one observer. The reflexes showed the following: exaggerated Achilles bilaterally; radials, biceps and triceps equal and active. The left knee jerk was present, though sluggish; the right absent. A definitely positive Babinski test was present on the left, absent on the right. There was no ankle clonus. Vibratory sensation was undisturbed; there was some hyperesthesia of the lower extremities. The uterus was slightly enlarged but showed no evidence of fibromyomata or disease of the cervix. Blood pressure was 115 systolic, 50 diastolic. Temperature was 99.8° F. in the afternoon.

*Laboratory examinations* were as follows: Wassermann, Kahn, and Hinton tests negative; gastrointestinal Roentgen ray series negative except for questionable adhesions in the right lower quadrant of the abdomen; barium enema negative; plain plates of the kidneys, ureters, and bladder negative; cholecystograms by the dye method negative; Roentgen rays of all the long bones, vertebræ, skull, and chest negative. A large number of urine specimens were normal; four stools showed no occult blood. Icteric index was 4. Gastric analysis with 7 per cent alcohol test meal followed in 45 minutes by 0.5 mg. of histamin in solution showed no free hydrochloric acid 1 hour after histamin was given and a total acidity of 4 at the same period; the volumes of gastric juice obtained were exceedingly low. Blood studies on July 1 and 2 showed the following: hemoglobin, 20 per cent (Dare and Sahli); red blood cell count, 2.7 and 2.3 million per cu. mm.; white blood cell count, 3700 and 4050 per cu. mm.; polymorphonuclears, 45 per cent; lymphocytes, 51 per cent; monocytes, 0; eosinophils, 4 per cent; basophils, 0. Red blood cells showed very marked achromia, extreme change in size and shape with small cells predominating and little or no polychromatophilia. Average red blood cell diameter was 6.02 micra, the cells varying from 3 to 7 micra. The blood platelet count was 154,000 per cu. mm. by a pipette method—267,000 per cu. mm. by the author's indirect method.\* Reticulocytes numbered 0.7 per cent. The remainder of the blood counts are given in Table I.

*Bone-marrow Biopsy.* A biopsy of the sternal bone-marrow was performed on July 10. This showed an exceedingly hyperplastic marrow. It was crowded with large numbers of nucleated red cells, the white blood cell forming elements being diminished. The characteristic feature of the

\* To be published. It involves the use of a stain for making the blood platelets visible and counting them under oil immersion.

TABLE 1.—CASE 1. HELEN H.

Date.	Hemo- globin, per cent; D = Darc, S = Sahli.	Red blood cells, millions cu.mm.	White blood cells, per cu.mm.	Platelets, per cu.mm.; D = indirect method.	Reti- culo- cytes, per cent.	Poly- mor- pho- ni- clears, per cent.	Lymph- ocytes, per cent.	Mono- cytes, per cent.	Eosin- ophils, per cent.	Baso- phils, per cent.	Dosage and remarks.
July 1, 1930	20 (D)	2.7	3700	I 247,000 D 151,000	0.7	9	90	1.0	0	0.0	Achromia ++++; anisocytosis ++++; poikilocytosis ++++; polychromatophilia 0; 3 normoblasts seen in counting 100 white blood cells; platelets appear slightly decreased; average red blood cell diameter = 6.02 micra.
July 2, 1930	15 (S)	2.47	3200			43	44	13.0	..	..	
July 5, 1930	20 (D)	2.3	3600	I 488,800 D 370,000	2.0	38	54	2.0	5	1.0	Liver extract, 4 vials daily begun.
July 8, 1930	15 (S)	1.88	6300			..	..	..	..	..	
July 10, 1930	18 (D)	2.8	6700	I 442,000 D 182,000	3.4 1.8	..	..	..	..	..	Anisocytosis ++++, with microcytes—occasional fairly large cells; poikilocytosis ++++; polychromatophilia; platelets often large and bizarre.
July 14, 1930	13 (S)	2.46	2900			..	..	..	..	..	
July 15, 1930	20 (D)	2.9	2500	I 218,000 D 220,000	5.2 0.6	..	..	..	..	..	Liver extract discontinued. Ferre and ammonium citrate 3 gm. daily begun.
July 16, 1930	13 (S)	2.26				..	..	..	..	..	
July 17, 1930	20 (D)	2.9	3100	I 483,000 D 264,000	4.6 2.4	..	..	..	..	..	Achromia ++++; marked anisocytosis with good many large cells well filled with hemoglobin; poikilocytosis ++++; polychromatophilia ++.
July 18, 1930	15 (S)	3.22				..	..	..	..	..	
July 20, 1930	15 (D)	2.68	5100	I 250,000 D 164,000	3.2 5.8	..	..	..	..	..	Ferre and ammonium citrate 6 gm. daily; average red blood cell diameter 5.94 micra; achromia ++; anisocytosis ++++; polychromatophilia 0.
July 21, 1930	15 (S)	1.96		I 465,000 D 310,000	6 7	..	..	..	..	..	
July 30, 1930	35 (S)	2.01	5600	I 255,000 D 254,000	0.4	64	21	8.0	6	1.0	Achromia ++++; marked anisocytosis with good many large cells well filled with hemoglobin; poikilocytosis ++++; polychromatophilia ++.
August 2, 1930	37 (S)	3.38	4600			..	..	..	..	..	
August 3, 1930	40 (S)	3.17	4600	I 318,700 D 232,000	0.8	..	..	..	..	..	Achromia ++++; marked anisocytosis with good many large cells well filled with hemoglobin; poikilocytosis ++++; polychromatophilia ++.
August 5, 1930	46 (S)	3.95	....	I 1,169,000 D 424,000	9.6	..	..	..	..	..	
August 13, 1930	51 (S)	3.99	6000	I 1,707,000 D 458,000	2.8	..	..	..	..	..	Achromia ++++; marked anisocytosis with good many large cells well filled with hemoglobin; poikilocytosis ++++; polychromatophilia ++.
August 18, 1930	56 (S)	4.36	6500	I 509,000 D 205,000	1.0	..	..	..	..	..	
August 30, 1930	63 (S)	4.86	5500	I 602,000 D 252,000	1.2	51	25	14.5	9	0.5	Achromia ++++; marked anisocytosis with good many large cells well filled with hemoglobin; poikilocytosis ++++; polychromatophilia ++.
September 6, 1930	77 (S)	4.45	6100	I 489,000 D 300,000	1.0	..	..	..	..	..	
October 20, 1930	88 (S)	4.61	6500	I about 2,000,000	0.0	..	..	..	..	..	

marrow was the large number of erythroblastic islands composed of cells about  $1\frac{1}{2}$  the size of the normoblast, with a grayish, fairly abundant cytoplasm and a round nucleus which contained coarse masses of chromatin. Numerous transitions between these erythroblasts and the typical normoblasts were seen. No megaloblasts were found.

*Clinical Course.* On admission, the patient was given a 4000 calorie diet with liver. However, she ate only about one-half of this so that during her stay in the hospital, she gradually lost weight. Liver was discontinued after the first day. The afternoon temperature was constantly elevated to  $99.8^{\circ}$  F., the pulse ranging between 80 to 100 per minute. Beginning with July 10, she was regularly given 4 vials of liver extract daily (Lilly No. 343) until July 20 without clinical or hematologic improvement. In fact, the anemia, especially the percentage of hemoglobin, became slightly more severe during this period, as shown on Chart I. On July 21, she was discharged from the hospital against advice. Before discharge, however, she was advised to take ferric and ammonium citrate in doses of 1 gm. 3

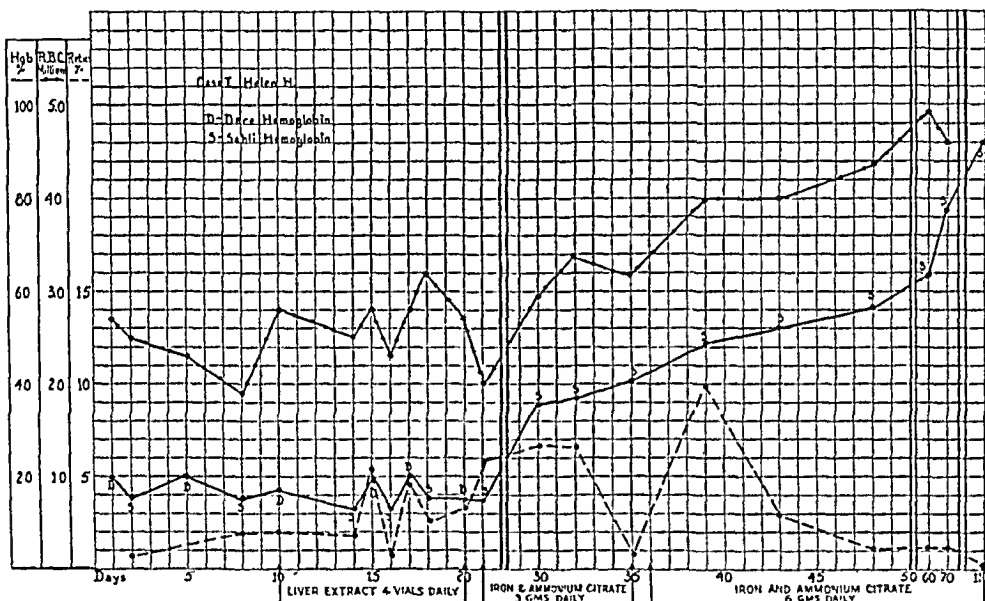


CHART I.

times daily (in 25 per cent aqueous solution), and to continue with her regular diet. On July 21, the date of discharge, hemoglobin was 15 per cent; red blood cell count, 1,960,000 per cu. mm.; white blood cell count, 5100 per cu. mm. She returned to the blood clinic on July 30, 9 days after discharge. She had felt no change for 3 days after starting the iron. However, on the fourth day, she awoke feeling a great deal better and with a desire to eat. She began to eat ravenously on that day and continued to do so. Her tongue became less sore and the numbness and tingling of the fingers became diminished. There had been a marked rise in hemoglobin and erythrocyte count in this 9-day period, hemoglobin having risen from 15 per cent to 35 per cent and the red blood cell count almost a million per cu. mm. The reticulocytes were increased to 6.7 per cent, but it is probable that the height of the reticulocyte response had been passed. Polymorphonuclear and platelet counts had also shown a definite increase. In the next few days, there was but little change: as a matter of fact, the leukocyte and platelet counts had fallen. The dosage of ferric and ammonium citrate

was therefore doubled to 6 gm. daily. In a week there was another marked response, so that on August 9, hemoglobin was 46 per cent, erythrocyte count 3,950,000 per cu. mm. Blood platelets had reached the astonishing level of 1,200,000 per cu. mm. and reticulocytes numbered 9.6 per cent. Her tongue bothered her no longer; she could now tolerate even vinegar. There were no paresthesias. Appetite continued to be ravenous so that she ate almost constantly. There was no weakness or dyspnea. She was gaining considerable weight, and her color was now quite pink. She said that she now felt better than she had for years. From that time on there was continued clinical and hematologic improvement. On October 29, hemoglobin was 88 per cent; red blood cell count, 4,640,000 per cu. mm.; white blood cell count, 6500 per cu. mm.; blood platelet count, 600,000 per cu. mm.; reticulocytes, 0 per cent. She had voluntarily discontinued iron therapy about a month previously. There was remarkable clinical improvement. Her face was extremely red, almost plethoric. She was now quite robust, her weight being 158 pounds.

**Summary of Case 1.** A woman aged 44 developed in 1925 dyspnea, weakness, loss of weight, diarrhea and marked pallor; she was found by a doctor to be anemic, was given iron and became much improved. In 1926, however, the symptoms recurred, but she again took iron and again became improved. In 1928, there was a third relapse; she took no iron at this time, however; symptoms became progressively worse so that in December, 1929, she could hardly walk about. At this time she developed marked soreness of the tongue and paresthesias of the fingers and toes. In July, 1930, she came to the Beth Israel Hospital for treatment. She presented a very severe anemia of the "secondary" type for which, however, no cause could be found. Tongue was smooth; there were signs of "combined system disease." Gastric analysis showed no free hydrochloric acid even after histamin. Bone-marrow biopsy disclosed crowding of the marrow with erythro- and normoblasts. The erythroblasts were present in islands. There was no response to liver extract. On taking large doses of iron and ammonium citrate there was immediate and striking response so that in the course of 3 months she became entirely well. Hemoglobin rose in this period from 12 to 88 per cent; red blood cell count from 1,960,000 to 4,640,000 per cu. mm.; white blood cell count from 3200 to 6500 per cu. mm. There were definite reticulocyte and platelet responses.

It was felt that this patient had pernicious anemia, although of an unusual type. The subjective symptoms were typical of that disease, *i.e.*, recurring anemia associated with diarrhea, anorexia and weakness, sore tongue, paresthesias. Except for the lack of icterus which in the ordinary type of pernicious anemia is due to break-down of red blood cells, the objective signs were also typical: extreme pallor, a very smooth tongue with atrophied papillae, and the signs of "combined system disease." The gastric analysis with its lack of free hydrochloric acid after histamin was typical. The blood studies showing anemia, leukopenia, relative lymphocytosis, monocytopenia, and slight thrombocytopenia were consistent with

the ordinary ease of pernicious anemia. However, the red blood cells were smaller than normal and poorly filled with hemoglobin—in other words, there was microcytosis with hypochromia and a color index under 1 as opposed to ordinary pernicious anemia in which there is macrocytosis and hyperchromia and a color index over 1. The bone-marrow, despite the anemia was crowded with erythroblasts and normoblasts: this too was reminiscent of the bone-marrow of pernicious anemia, which despite the anemia is crowded with megaloblasts. For reasons cited below, it was felt that this patient had pernicious anemia, but of an unusual type—dependent upon an erythronormoblastic or normal response of the marrow rather than upon a megaloblastic or embryonic response.

CASE 2.—B. I. H., No. 971. J. W., a married pipe fitter, aged 29 years, a native of this country (Maine) was admitted to the Beth Israel Hospital for study of his anemia on December 19, 1928. Family history was unimportant; he was separated from his wife. Born in Maine, he had always lived in New England. Until recently he had been a pipe fitter but had lately become a metal worker and occasionally came in slight contact with lead. Six years previously he had contracted gonorrhea and shortly thereafter developed "rheumatism." In March, 1927, while working in Berlin, New Hampshire, he developed "grippe," which was followed by increasing weakness, loss of weight and pallor. He consulted a doctor who told him he was anemic and gave him subcutaneous injections. Anemia persisting, however, he consulted in October, 1927, another physician who found he "had no blood at all." This physician in writing to the Beth Israel Hospital in 1928, said that the patient "presented the characteristic symptoms of pernicious anemia with the typical blood picture." He accordingly gave the patient liver, iron pills and acid, with resultant rapid improvement in both the subjective symptoms and the anemia. Hemoglobin rose from 35 to 85 per cent. For about a year the patient felt better, but during October, 1927, he again developed weakness, dyspnea, severe headache, loss of weight, lack of color, and pulling sensation in the legs. These symptoms rapidly grew worse so that he finally came to the Boston Dispensary and was referred to the Beth Israel Hospital for study. He gave no history of bleeding from any source, nor had he varied in his dietary habits, which were normal. On examination he was found to have white pallor, no icterus being present. The eyes were brown, the hair of the same color. The lower eyelids were slightly puffy. Tongue was smooth, the papillæ at the edges atrophied. Lungs were normal. Heart, except for a heaving impulse and a soft blowing systolic murmur at the apex, was normal. Blood pressure was 128 systolic, 68 diastolic. Neither liver nor spleen were felt. Lymph nodes were not enlarged. The reflexes were normal.

*Laboratory Data.* The blood showed a marked degree of "secondary" anemia: *i. e.*, hemoglobin was 42 per cent (S); red blood cell count, 3,470,000 per cu. mm.; color index, 0.67; white blood cell count, 4400 per cu. mm.; blood platelets, 100,000 per cu. mm.; reticulocytes, 0.8 per cent. The red blood cells showed marked achromia with many microcytes; average red blood cell diameter was 6.14, variation from 3.6 to 8.0 micra. There was considerable poikilocytosis, but no polychromatophilia or basophilic stippling. One normoblast was seen in counting 100 leukocytes. The polymorphonuclear cells numbered 59 per cent, lymphocytes, 23 per cent; monocytes, 11 per cent; eosinophils, 3 per cent, and basophils, 4 per cent. Blood platelets seemed diminished on blood smear.

TABLE 2.—CASE 2. JAMES W.

[illegible]

Roentgen rays of the chest, sinuses, kidneys, teeth and gastrointestinal tract were all negative. Several urines were negative as were several stools tested for occult blood. The blood and spinal fluid Wassermann reactions were negative. Mosenthal test showed normal variation in specific gravity; 'phthalein excretion was 40 per cent in 2 hours. The spinal fluid was entirely normal. The basal metabolic rate was + 10 per cent. Gastric analysis on December 23 showed no free hydrochloric acid in the fasting contents, but 45 minutes after a test meal, 24 units of free hydrochloric acid was present.

*Bone-marrow biopsy* (sternum) was performed on December 31, 1928. This showed crowding of the marrow with erythro- and normoblasts, about 5 nucleated red cells to each white cell (normal about 1 to 1) being present. Only a few questionable megaloblasts were seen.

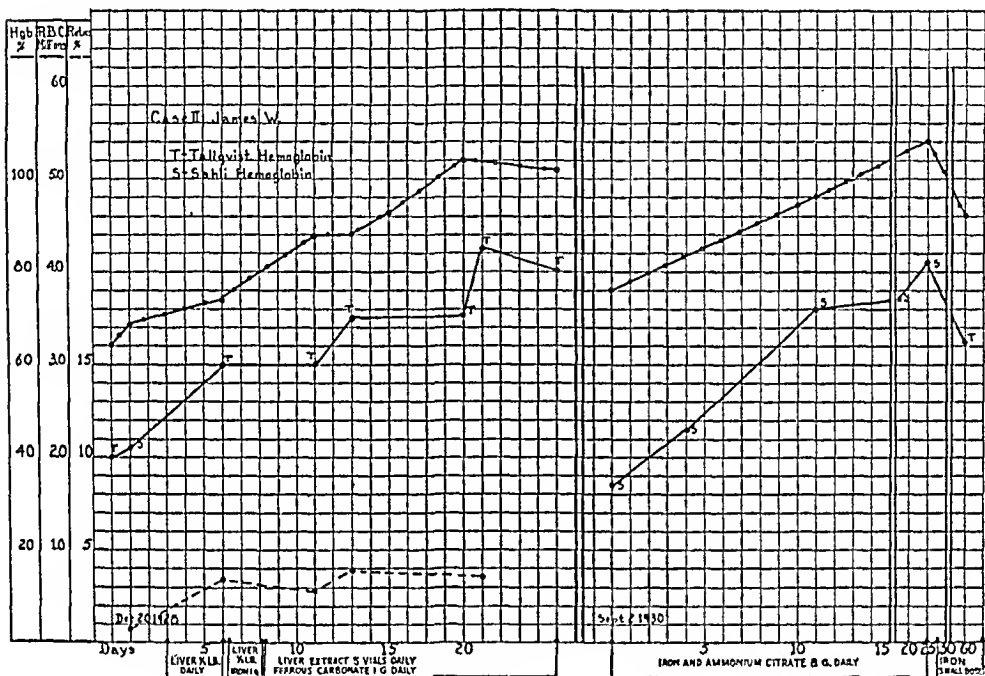


CHART II.

*Clinical Course.* It was originally felt that the anemia was secondary to some disorder such as hypothyroidism, nephritis, chronic infection, malignancy, etc., but apparently all of these possibilities were ruled out by the above findings. The suggestion was raised at that time by the author as to whether this might not be "a primary anemia of a secondary type (chlorosis?)."

On December 23, 1928, the patient was started on about  $\frac{1}{2}$  pound of liver daily in addition to the regular house diet. On December 26, he was given in addition ferrous carbonate 1 gm. daily. On December 28, liver was discontinued (the iron still being retained), and he was given 5 vials of liver extract (Lilly's No. 343) daily. It was difficult at the time to evaluate which of these methods of treatment was responsible for the subsequent rapid improvement. The patient rapidly improved, as will be seen from Chart II and was discharged from the hospital on January 15, 1929. At this time hemoglobin was 80 per cent (T); red blood cell count, 5,100,000 per cu. mm.; white blood cell count, 9400 per cu. mm.; polymorphonuclears, 71 per cent. There had been slight reticulocyte rise.



He was not heard from until almost 2 years later, when, on September 2, 1930, he was referred to the author for treatment of his anemia. He had felt well until August, 1930, at which time he developed a slight urethral discharge. This was treated by a physician with prostatic massage and silver nitrate irrigations of the bladder with subsequent relief. However, he soon developed aching pain in numerous muscles and became rapidly weak, pale, listless, and dyspneic. Frontal headache was intense. He claimed his appetite was poor, yet he managed to eat daily the following breakfast—two eggs, oatmeal, milk, toast, coffee; lunch—sandwiches, fruit; supper—soup, meat, green vegetables, pastry. He had lost a few pounds in the past few weeks. Weakness forced him to quit work. Examination was negative except for marked pallor, some stiffness of the dorsal spine, and smoothness of the tongue. Hemoglobin was 38 per cent (S); red blood cell count, 3,800,000 per cu. mm.; white blood cell count, 5600 per cu. mm. For 3 weeks prior to consulting the writer, he had been eating at least a  $\frac{1}{2}$  pound of liver daily, but despite this had been growing progressively weaker and paler. He was accordingly advised to discontinue the liver and to take ferric ammonium citrate in doses of 2 gm., 4 times daily (8 gm. daily). He began to take this medication on September 3. He awoke on the morning of September 5, feeling much better, "different." His appetite became ravenous so that after eating a large "steak supper," he again felt hungry in 2 hours. His blood picture improved almost miraculously, the hemoglobin rising in 3 days to 46 per cent, in 11 days to 72 per cent, in 25 days to 82 per cent. The headache, weakness, dyspnea, pallor disappeared quickly, but the patient complained bitterly of pains in his joints. The spine was quite stiff ("poker spine"), as was the lower back. He was accordingly given 3 injections of typhoid vaccine intravenously at weekly intervals. Although these gave transient relief, there was very little permanent response. On November 1, 1930, he looked rather poorly. Arthritis had been severe, preventing sleep at times. Tongue had become sore in the past 2 weeks. He had been taking the iron medication rather irregularly, from 2 to 6 gm. daily. There was some weight loss (to 134 pounds). Hemoglobin was 65 per cent (T), a distinct drop. Heat, massage, physiotherapy, etc., were advised.

**Summary of Case 2.** A 29-year-old American developed severe anemia (said to be pernicious anemia) in 1927. This was treated with liver and iron, with recovery. In 1928, there was a relapse of anemia. Examination disclosed a "secondary" type of anemia: hemoglobin, 42 per cent; red blood cell count, 3,470,000 per cu. mm.; white blood cell count, 4400 per cu. mm.; hypochromia and an average red blood cell diameter of 6.14 micra. No cause for this "secondary" anemia could be found. Gastric analysis showed free hydrochloric acid after a test meal. Bone-marrow biopsy, despite the anemia, disclosed crowding of the marrow with erythro- and normoblasts. There was prompt response to a mixed treatment of liver, iron, and liver extract. The patient felt well for almost 2 years, but again became weak, dyspneic and pale in August, 1930. On September 2, blood showed hemoglobin, 38 per cent; red blood cell count, 3,800,000 per cu. mm. He had been taking at least  $\frac{1}{2}$  pound of liver daily for 3 weeks; in spite of this pallor had been growing steadily worse. Liver was discontinued and he was given iron and ammonium citrate in doses of 8 gm. daily. There was prompt response, so that

on September 27 (24 days after beginning treatment) hemoglobin was 82 per cent and red blood cell count was 5,400,000 per cu. mm. However, although his strength, color and appetite became normal, arthritis persisted, preventing sleep at times. He lost weight, developed a sore tongue, took his medication irregularly. On November 1, 1930, hemoglobin was 65 per cent (T), and red blood cell count 4,600,000 per cu. mm. In this case, then, there were 3 relapses of severe anemia which, during the first relapse was considered to be "pernicious," during the second, was thought to be a peculiar type of "secondary" anemia, but which was at the third relapse considered to belong to a disease entity closely resembling pernicious anemia clinically, and probably an unusual type of pernicious anemia with a normoblastic rather than a megaloblastic marrow.

CASE 3.—B. I. H., No. 3254. B. S., a housewife, aged 23 years, a native of Russia, was admitted to the Beth Israel Hospital on July 26, 1929, for study of anemia. Family history was unimportant. She said she had been more or less pale since infancy and had never been very strong. She had had since infancy attacks of diarrhea which were ordinarily associated with marked pallor. At the age of 15 she was admitted to a Russian hospital for study of anemia which was associated with a "big stomach." She was given 16 subcutaneous injections, and medicine by mouth. Pallor disappeared within the course of 2 months. However, a year later, being faced with a good deal of housework, she again became pale, again entered the same hospital, and was again relieved. She was well from that time until 6 months after the birth of her first child in January, 1929, when she again became weak, pale, and increasingly dyspneic. Her appetite became very poor. There was occasional tingling of the fingers but no burning of the tongue. Examination disclosed marked pallor. The tongue was smooth at the edges, the papillae not being visible. The liver was questionably felt at the right costal margin; the spleen was not felt. Skin showed fairly numerous ecchymoses and petechiae. Reflexes were normal.

*Laboratory Data.* On admission hemoglobin was 35 per cent (T); red blood cell count, 2,100,000 per cu. mm.; white blood cell count, 3240 per cu. mm.; polymorphonuclears, 54 per cent; lymphocytes, 40 per cent; monocytes, 5 per cent; eosinophils, 1 per cent. On July 30 the blood platelets were much reduced, being 44,000 per cu. mm., by a pipette method and 56,280 per cu. mm., by the author's indirect method. Reticulocytes numbered 1.5 per cent; polymorphonuclears were 30 per cent; lymphocytes, 54 per cent; monocytes, 9 per cent; eosinophils, 5 per cent; basophils, 2 per cent. The red blood cells showed extreme change in size with many microcytes; average erythrocyte diameter was 5.72 micra, variation from 3 to 10 micra. There was marked achromia, marked change in shape and slight polychromatophilia. The blood platelets were much reduced on blood smear. Bleeding time was 12.5 minutes, definitely increased; coagulation time 2½ minutes; clot retraction was fair. Fragility test was within normal limits—hemolysis beginning at 0.46 per cent of sodium chlorid and being complete at 0.36 per cent. Several urines and stools were normal. The Mosenthal test showed good variation in specific gravity. Icteric index was 4. Gastric analysis showed no free hydrochloric acid in the fasting contents; 1 hour after a test meal there was 1 unit of free hydrochloric acid present, total acidity being 8. Gastrointestinal Roentgen rays showed at first an irregular duodenum suggesting ulcer, but after the subcutaneous

TABLE 3.—CASE 3. BESSIE S.

Date.	Hemo- globin, per cent.	Red blood cells, millions per cu. mm.	White blood cells, per cu. mm.	Blood platelets, per cu. mm.	Reticu- locytes, per cent.	Poly- morpho- nuclear cells, per cent.	Lympho- cytes, per cent.	Mono- cytes, per cent.	Eosino- phils, per cent.	Baso- phils, per cent.	Dosage and remarks.
July 26, 1929 . . .	35 (T)	2.1	3240	.....	...	54	40	5	1	...	Iron and ammonium citrate, 6 gm. daily begun.
July 29, 1929 . . .	...	2.5	...	I 56,280	1.5	34	54	5	5	2	
July 30, 1929 . . .	...	2.68	...	D 44,000	...	...	...	...	...	...	
August 1, 1929 . . .	...	2.7	...	.....	...	...	...	...	...	...	Crowded with platelets.
August 4, 1929 . . .	...	...	...	.....	...	...	...	...	...	...	
August 7, 1929 . . .	...	2.49	8150	.....	6.0	59.5	31.5	3.5	3.5	2	
August 10, 1929 . . .	...	...	...	I 1,375,000	4.8	54	33	8	4	1	Iron discontinued. Reduced iron 4 gm. daily. Liver, ½ pound daily, and iron.
August 11, 1929 . . .	41 (S)	2.87	5040	.....	...	70	22	6	1	1	
August 12, 1929 . . .	46 (S)	3.38	4320	.....	...	62	29	6	3	0	
August 13, 1929 . . .	...	...	6550	.....	...	...	...	...	...	...	Iron almost completely discontinued. Iron discontinued.
August 23, 1929 . . .	60 (S)	3.41	6400	.....	...	38	42	12	6	2	
September 6, 1929 . . .	60 (S)	3.415	6200	I 884,000	0.4	...	...	...	...	...	
September 20, 1929 . . .	45 (S)	3.1	7500	D 395,000	1.2	40	35.5	13.5	10	1	Iron and ammonium citrate 3 gm. daily. { Iron and ammonium citrate 3 gm. and copper sulphate 0.1 gm. daily. Copper sulphate 0.05 gm. daily. Iron same dose.
October 4, 1929 . . .	40 (S)	4.27	...	D 154,000	0.9	52	27.5	11.5	8	1	
November 1, 1929 . . .	45 (S)	4.58	...	D 248,000	0.6	...	...	...	...	...	
November 15, 1929 . . .	48 (S)	4.6	...	I 1,228,000	...	...	...	...	...	...	Iron almost completely discontinued. Iron discontinued.
December 6, 1929 . . .	46 (S)	4.6	...	D 774,000	...	...	...	...	...	...	
December 27, 1929 . . .	50 (S)	4.59	...	D 378,000	...	...	...	...	...	...	
January 24, 1930 . . .	52 (S)	4.55	...	I 428,000	...	...	...	...	...	...	Iron and ammonium citrate 3 gm. daily. { Iron and ammonium citrate 3 gm. and copper sulphate 0.1 gm. daily. Copper sulphate 0.05 gm. daily. Iron same dose.
April 18, 1930 . . .	43 (S)	4.16	...	D 262,000	0.4	...	...	...	...	...	
May 21, 1930 . . .	45 (S)	4.05	...	I 407,000	1.3	...	...	...	...	...	
November 12, 1930 . . .	...	...	...	D 320,000	...	...	...	...	...	...	Iron and ammonium citrate 3 gm. daily. { Iron and ammonium citrate 3 gm. and copper sulphate 0.1 gm. daily. Copper sulphate 0.05 gm. daily. Iron same dose.
February 18, 1931 . . .	55 (S)	4.21	...	I 810,000	...	...	...	...	...	...	
April 16, 1931 . . .	68 (S)	4.75	...	.....	...	...	...	...	...	...	
July 21, 1931 . . .	82 (S)	5.25	...	.....	...	...	...	...	...	...	

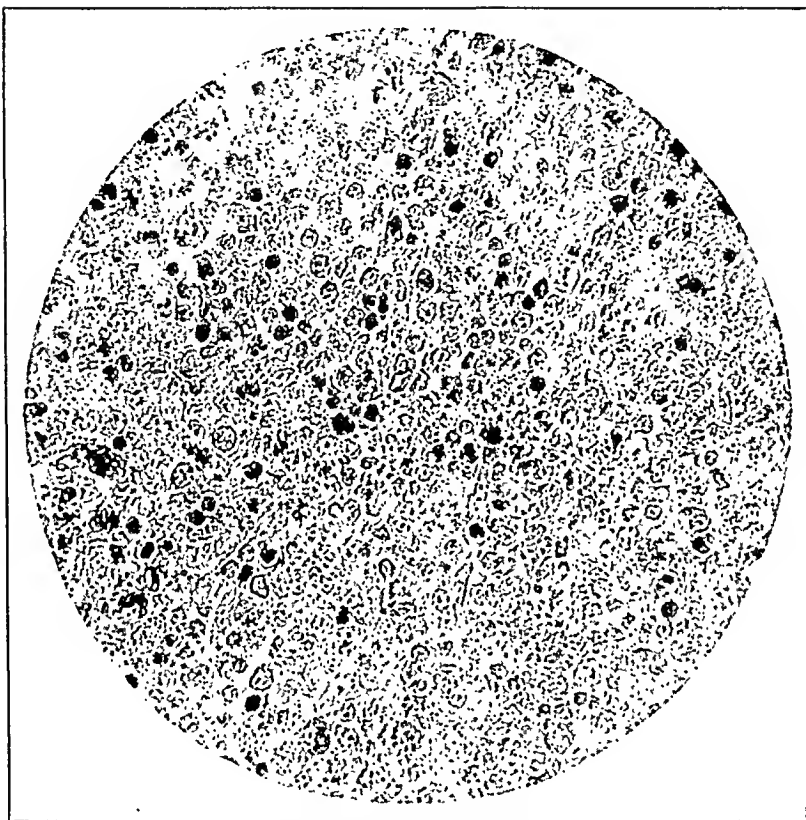


FIG. 1.—(C)—Photomicrograph of sternal bone-marrow biopsy. Case 1, July 10, 1930.  $\times 600$ . Note the exceedingly hyperplastic marrow despite the extreme anemia (hemoglobin 15 per cent, red blood cell count 2,000,000). The large majority of the cells are pale staining erythroblasts, among which are interspersed the more mature normoblasts with pyknotic nuclei.

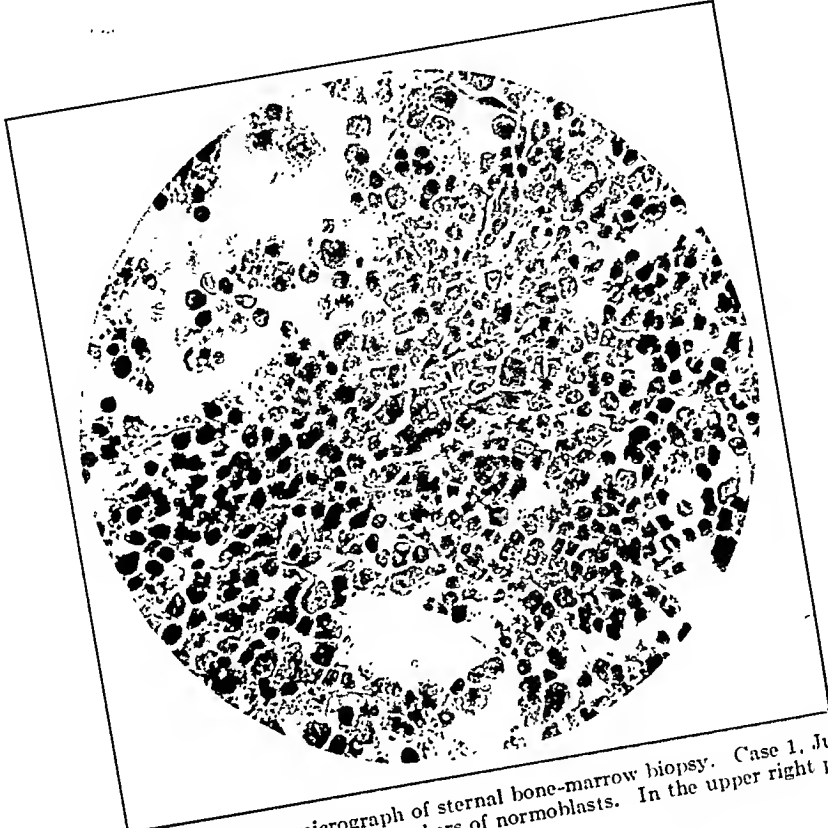


FIG. 2.—(B)—Photomicrograph of sternal bone-marrow biopsy. Case 1, July 10, 1930.  $\times 600$ . Note the large numbers of normoblasts. In the upper right portion of the field is an island of white cell-forming tissue.

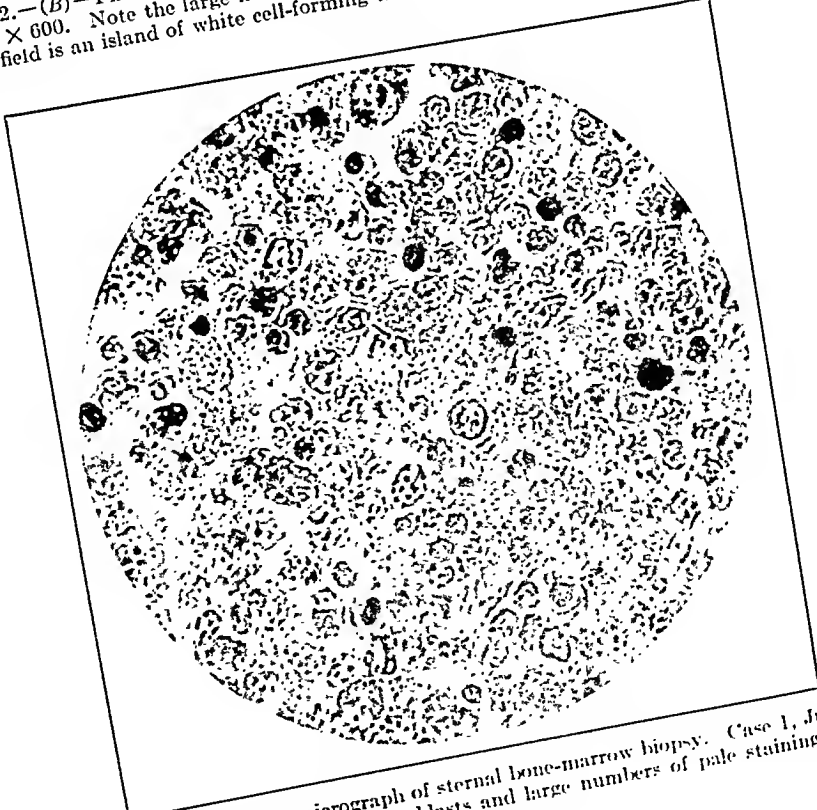


FIG. 3.—(A)—Photomicrograph of sternal bone-marrow biopsy. Case 1, July 10, 1930.  $\times 1200$ . Numerous normoblasts and large numbers of pale staining, more primitive, nucleated red cells, i. e., erythroblasts.

injection of atropin this irregularity disappeared leading to a roentgenologic diagnosis of a normal gastrointestinal tract. Bone-marrow biopsy on July 31, 1929, disclosed, despite the severe anemia, a marrow crowded with erythro- and normoblasts, many more being present than normally. Three hundred nucleated red cells were seen simultaneously with 160 white cells, a ratio of 3 to 1.6, abnormally high (normal about 1 to 1). Of these nucleated red cells, 59.3 per cent were normoblasts, 37.0 per cent erythroblasts, and 3.7 per cent megaloblasts. Two megakaryocytes were seen in this count.

*Clinical Course.* On August 4, 1929, iron and ammonium citrate in doses of 2 gm., 3 times daily were begun. This resulted in rapid clinical and hematologic improvement. Reticulocyte count, white blood cell count, polymorphonuclear count, platelet counts all showed prompt rises. On August 7, although there was no rise in red blood cell count, reticulocytes had risen to 6 per cent and blood platelets were now very abundant. On August 11, the blood smears were found crowded with platelets; on actual count they numbered 1,375,000. Ecchymoses and petechiae

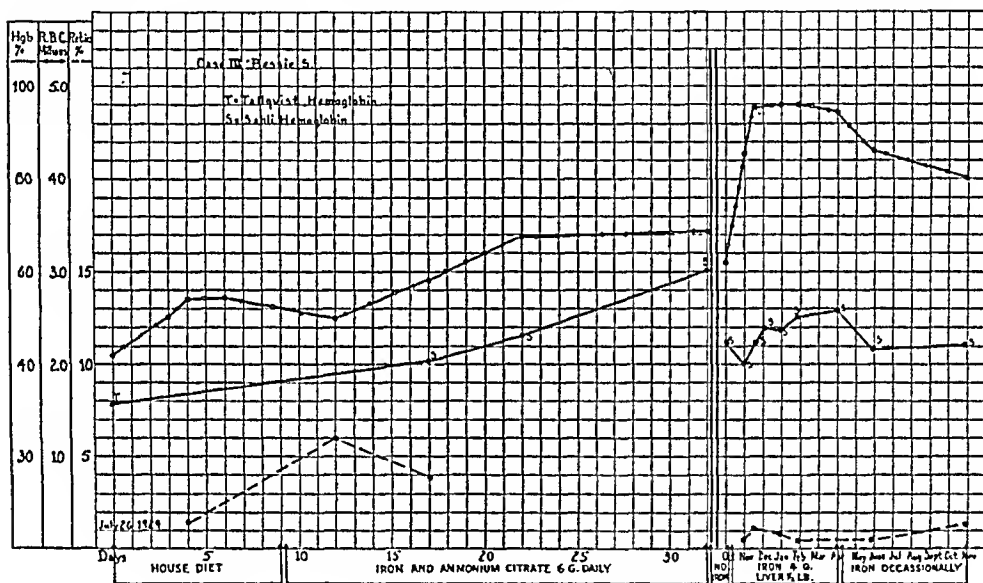


CHART III.

promptly disappeared. Soon there was rise in both hemoglobin and red blood cell count, so that on September 6, hemoglobin was 60 per cent (T), and red blood cell count 3,410,000 per cu. mm. She returned in October, however, feeling rather poorly again; she had discontinued the iron solution to great extent because of a dislike for its taste. She was accordingly given reduced iron in doses of 2 gm. twice daily, and later advised to eat  $\frac{1}{2}$  pound of liver daily. There was fairly good response to this therapy from that time on until the following spring, although the red blood cell count showed a much greater rise than did the hemoglobin which persisted at about 50 per cent. On May 21, 1930, she showed again a definite drop in counts and was advised again to continue with iron medication which she had almost completely discontinued. She was not seen again until November 12, 1930, when she again came to the clinic. She had discontinued iron medication several months previously. Hemoglobin had again dropped. Iron was again begun but without much change in counts. When copper sulphate was combined with the iron medication, there was striking response.

## DAMESHEK: PRIMARY HYPOCHROMIC ANEMIA

**Summary of Case 3.** A woman, aged 23 years, had been pale since infancy. From the ages of 1 to 13 she had been subject to relapses of diarrhea and pallor. At 15 and 16 years of age she had severe relapses of anemia, necessitating treatment in a hospital. In July, 1929, 6 months after delivery of her first child, she became weak, dyspneic, and pale. Examination disclosed a very pale woman without icterus and with smooth atrophied tongue. Ecchymoses and petechiae were common. Blood showed a marked "secondary" type of anemia; hemoglobin was 35 per cent (T); red blood cell count was 2,100,000 per cu. mm.; white blood cell count 3240 per cu. mm. There was relative lymphocytosis and marked reduction in blood platelets with increase in bleeding time. No cause could be found for this "secondary" anemia. Gastric analysis showed almost no free hydrochloric acid after first test meal. Bone-marrow biopsy disclosed a hyperplastic marrow crowded with erythro- and normoblasts despite the severity of the anemia. There was striking response to iron therapy in large doses, but when this was discontinued there was definite relapse which was checked by further iron therapy. She took iron medication very irregularly and there were definite relapses. Liver therapy combined with the iron at one time seemed to aid erythrocyte response. The percentage of hemoglobin tended to remain stationary at about 50 per cent. Upon the addition of copper sulphate, hemoglobin rose steadily to 82 per cent. Remissions were accompanied by definite increases in reticulocytes and outpouring of platelets in large numbers. It was felt that this was another instance of primary hypochromic anemia, and possibly a type of pernicious anemia associated with an erythronormoblastic marrow rather than with one of the ordinary megaloblastic type.

**CASE 4.**—O. P. D., No. 11799. Mary C., a housewife, aged 37 years, a native of Scotland, came to the outpatient department on May 15, 1930, complaining of weakness which had been present since January, 1930. Family history was unimportant. She had been married 15 years, her husband and 3 children being alive and well. She had been well until 1923 when a miscarriage occurred. At that time she became pale, although the loss of blood was slight. Chronic backache developed. In 1929 she developed numbness and tingling of the fingers and numbness of the entire face, especially on the right. Her appetite had always been quite poor. She claimed that meat made her choke. As a result she had not eaten meat for 10 years or more, her dietary otherwise being satisfactory. She admitted being of the nervous type, easily irritated, easily worried. Examination disclosed a light-haired, blue-eyed woman. Tongue was atrophied, being very smooth and glistening throughout. A soft systolic murmur was heard over the mitral area. The spleen was felt by one observer. The finger-nails showed definite "trophic" changes, being markedly cracked and deformed. Reflexes were normal; vibratory sensation was definitely diminished over the left leg, normal elsewhere. Blood pressure was 128 systolic and 75 diastolic. Gastric analysis showed no free hydrochloric acid in the fasting contents; 1 hour after Ewald test meal there was a faint trace of free hydrochloric acid, not enough to titrate. Blood Wassermann reaction

TABLE 4.—CASE 4.—MARY C.

Date.	Hemo- globin, per cent.	Red blood cells, millions per cu.mm.	White blood cells, per cu.mm.	Blood platelets, per cu.mm. I = indirect, D = direct.	Reticu- locytes, per cent.	Poly- morpho- nuclear cells, per cent.	Lymph- ocytes, per cent.	Mono- cytes, per cent.	Eosino- phils, per cent.	Baso- phils, per cent.	Dosage and remarks.
May 22, 1930 .	45 (S)	4.12	5,000	....	...	55.5	36.5	5	1.5	1.5	Iron and ammonium citrate 3 gm. daily.
June 26, 1930 .	55 (T)	4.5	5,500	....	...	63	36	1	...	...	Liver, $\frac{1}{4}$ pound daily plus iron.
July 31, 1930 .	55 (T)	4.34	...	....	...	...	...	...	...	...	Meat juices, etc.; discontinue liver.
September 17, 1930	58 (S)	4.74	...	I 520,000	0.4	69	24	7	...	...	Meat juices; discontinue iron.
September 24, 1930	68 (S)	4.77	7,400	D 218,000							
September 30, 1930	75 (S)	4.76									
October 14, 1930 .	4.66										
October 23, 1930 .	72 (S)	4.24									
November 12, 1930	72 (S)	4.35	10,000	I 810,000	0.6						

TABLE 5.—CASE 5. KATHERINE N.

Date.	Hemo- globin, per cent.	Red blood cells, millions per cu.mm.	White blood cells, per cu.mm.	Reticu- locytes, per cent.	Neutro- phils, per cent.	Lymph- cytes, per cent.	Mono- cytes, per cent.	Eosino- phils, per cent.	Dosage and remarks.
August 30, 1930	45 (S)	3.85	5600	...	58	30	9	1	Iron and ammonium citrate, 3 gm. daily.
September 3, 1930	...	...	...	...	...	...	...	...	Iron, 2 gm. daily.
September 8, 1930	48 (S)	...	...	...	...	...	...	...	
September 15, 1930	56 (S)	4.30	...	...	...	...	...	...	
September 23, 1930	56 (S)	5.10	...	...	...	...	...	...	
November 4, 1930	60 (S)	4.80	...	...	...	...	...	...	
December 16, 1930	68 (S)	5.10	...	...	72	14	10	...	Iron, 1 gm. daily.
February 17, 1931	96 (S)	6.20	...	...	...	...	...	4	



## DAMESHEK: PRIMARY HYPOCHROMIC ANEMIA

was negative. Hemoglobin was 45 per cent (S); red blood cell count, 4,120,000 per cu. mm.; white blood cell count, 5000 per cu. mm. Blood smear showed marked achromia of the red blood cells with moderate change in size and shape; microcytes were common; there was no polychromatophilia. Differential count of the white blood cells showed a relative lymphocytosis. The rest of the laboratory data are given in the chart.

On May 22, 1930, treatment with iron and ammonium citrate 3 gm. daily was begun. On May 29, 4 cc. of dilute hydrochloric acid was given before meals. On June 26, in addition to the above medications, she was given (by another physician)  $\frac{1}{2}$  pound of liver daily. She improved definitely, though slightly, on iron medication, but there was no response to added liver.

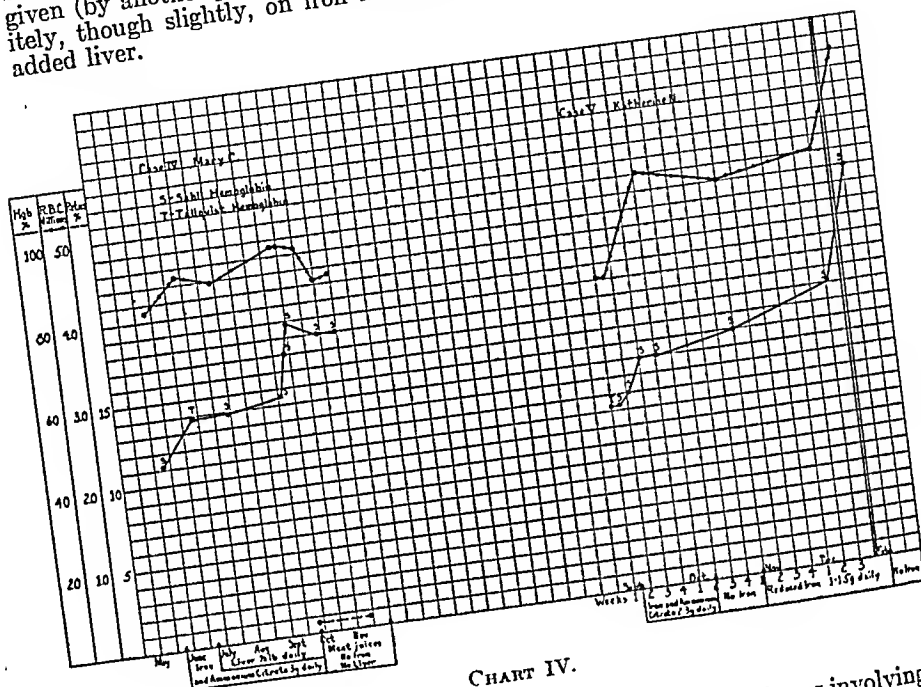


CHART IV.

On August 5, 1930, she developed suddenly a spell of numbness involving the right side of the entire body including the face; this may have been hysterical in nature as it appeared following a slight emotional upset.

On September 17, because of the history of lack of meat for 10 years, meat juices, purée of meat, scraped beef, and meat soup were started, the patient being requested to discontinue liver, iron, and hydrochloric acid. Through a misunderstanding, she continued on iron until September 24. There was marked improvement following inauguration of meat juices, even when iron was discontinued. However, this was not well sustained, so that on October 28 there was evidence of slight relapse.

**Summary of Case 4.** A Scotch-American housewife, aged 37 years, complained of backache, weakness, and paresthesia of the fingers, especially during the past year. She had not eaten meat for 10 years. Examination disclosed an atrophied tongue, pallor, and diminished vibratory sensation over the left leg. Gastric analysis

showed a faint trace of free hydrochloric acid after test meal. The blood showed a moderate degree of hypochromic anemia. Treatment with moderate doses of iron resulted in definite, though slight improvement; there was no improvement with liver; but on meat juices, etc., there was prompt increase in hemoglobin and red blood cell count. It was felt that this was a case of primary hypochromic anemia, a variant of the ordinary hyperchromic, macrocytic "pernicious" anemia.

CASE 5.—K. N., an American housewife, aged 37 years, was referred to the writer on August 30, 1930, by Dr. Maurice Evans of Boston, Massachusetts, for diagnosis and treatment. Family, marital, and past history were not significant. She complained of frequent head colds which were often accompanied by general aches and pains, sore throat, and slight fever, and persistent cough. She was nervous and easily upset. She felt constantly weak, tired, and without ambition. About a year previously she began to grow pale; shortly thereafter the tongue became itchy and very sore to acid fruits, etc. She had no gastric distress and there were no paresthesias of the extremities. She had always eaten a well-balanced diet with plenty of fruit, green vegetables, and meat; lately there had been marked loss of appetite, with some diminution in food intake. She had lost 10 pounds in weight in the past year.

Examination revealed a well-developed, rather thin woman, definitely pale. The pallor was "white" with no trace of jaundice to the skin or sclerae. The tongue was extremely smooth and glistening, with no visible papillae. There was no splenic or hepatic enlargement, and no masses were felt. Lymph nodes were not enlarged. Reflexes were hyperactive; there was no loss in vibratory sense. Blood pressure was 110 systolic and 60 diastolic. Urine was normal; stools showed no occult blood; Roentgen ray of the chest was negative. Gastric analysis showed no free hydrochloric acid 1 hour after the injection of 0.4 mg. of histamin subcutaneously. Blood Wassermann reaction was negative. Blood studies showed: hemoglobin, 45 per cent (T); red blood cell count, 3,850,000 per cu. mm.; white blood cell count, 5600 per cu. mm.; polymorphonuclear cells, 58 per cent; lymphocytes, 30 per cent; monocytes, 9 per cent; eosinophils, 1 per cent. There was moderate to marked hypochromia of the red blood cells with moderate change in size and shape and no polychromatophilia. The blood findings 4 days later were practically identical. On this day (September 3) she was started on iron and ammonium citrate, 2 gm. 3 times daily (but took doses of only 1 gm.). She was also requested to eat more food, particularly milk, between meals. On September 8, the tongue had practically ceased troubling her; she had gained 2 pounds in weight and hemoglobin had risen slightly to 48 per cent (S). She was asked to take 8 gm. of the iron and ammonium citrate daily, but this upset her so that she vomited and took the iron infrequently (about 2 gm. daily). On September 15, hemoglobin had risen to 56 per cent (S), and red blood cell count to 4,300,000 per cu. mm. She continued on 2 gm. of iron daily. On September 23, hemoglobin was 56 per cent (S) and red blood cell count 5,100,000 per cu. mm. On October 6, tonsillectomy was performed by Dr. Evans. She discontinued iron at this time. On November 4, hemoglobin was 60 per cent (S) and red blood cell count was 4,800,000 per cu. mm. She was advised to continue with 1½ gm. of iron daily. On December 16, hemoglobin was 68 per cent (S) and red blood cell count 5,100,000 per cu. mm. She felt entirely well. She continued to take 1 gm. of iron daily and on February 17, 1931, she showed the surprising figures of hemoglobin 96 per cent (S) and red blood cell count 6,200,000 per cu. mm.

**Summary of Case 5.** An American housewife, aged 37 years, complained of frequent cold, cough, weakness, pallor, and burning tongue. Examination disclosed marked white pallor; smooth atrophied tongue, large red tonsils. Gastric analysis disclosed no free hydrochloric acid after histamin was given. Blood showed a moderate hypochromic anemia which responded rather slowly, principally, it was felt, because the patient could not take the full dosage of iron as prescribed. There was definite rise, however, in hemoglobin and red blood cell count with disappearance of sore tongue, weakness, and fatigue. It was felt that this was another instance of a primary anemia of the hypochromic type.

**CASE 6.—B. I. H., No. 9751.** Rose O. M., a housewife, aged 28 years, of French-Canadian parentage, was referred to the writer for study by Dr. Reuben Guralnick of Boston. She entered the hospital at 4 A.M. of February 4, 1931, disoriented and irrational, with the story of having had a convulsion  $\frac{1}{2}$  hour previously. Family history obtained at a later date revealed that her father had "always" been pale and had died of "cancer" at 65 years of age. An aunt of hers (her father's sister), although otherwise well, had been noticeably pale for a great many years. The patient herself had been pale since childhood; this was common knowledge to herself and her family but nothing had been done about it since she had always been able to be up and about and do her work. There had been no periods of extreme pallor or weakness until the present. Appetite had always been excellent and there had never been burning of the tongue. In September, 1930, she was delivered of a healthy infant. Both the pregnancy and puerperium were entirely normal, only a small amount of blood being lost at the time of delivery. She was entirely well for the ensuing 4 months but suddenly 3 weeks before admission she became irrational—and fainted. For 3 days thereafter she felt unusually sleepy and extremely weak. On the day before admission she suddenly became "delirious" and appeared to be deaf. At 3.30 on the morning of admission she awoke from sleep trembling violently and completely irrational. She was immediately brought to the Beth Israel Hospital. Physical examination revealed a very pale woman, almost completely disoriented. She responded rationally to simple questions and commands; response, however, was slow and she appeared very drowsy. There was a questionable Kernig sign bilaterally, but no rigidity of the neck. The tongue was smooth at the edges, otherwise normal. The rest of the examination was entirely negative except for general hyperactivity of the reflexes. Lumbar puncture was done, a clear, colorless fluid containing 2 cells per cu. mm. being obtained. Disorientation rapidly cleared, so that by 2 P.M. of the day of admission, she was entirely rational and was able to enter into an extended discussion of her history. In searching for an emotional cause for the probable hysteria, it was found that since her delivery she had had no sexual relationship with her husband who was always "tired." It was intimated that this might be a factor for hidden concern.

Although encephalitis lethargica, tuberculous meningitis, syphilis of the central nervous system and postpuerperal psychosis were considered, these could finally be ruled out and the diagnosis of hysteria made. A study of her obvious anemia was now made. She was found to have a "secondary" type of anemia: hemoglobin, 48 percent; erythrocytes, 3,810,000 per cu. mm. The red blood cells showed moderate achromia and marked change in size and shape. No cause for this anemia could be found: vaginal and rectal examinations being entirely negative. Urine was normal; several stools

TABLE 6.—CASE 6. ROSE M.

Date.	Hemo- globin, per cent.	Red blood cells, millions per cu.mm.	White blood cells, per cu.mm.	Blood platelets, per cu.mm.	Reticulo- cytes, per cent.	Poly- morpho- nuclear cells, per cent.	Lympho- cytes, per cent.	Mono- cytes, per cent.	Eosino- phils, per cent.	Baso- phils, per cent.
February 4, 1931	48 (S)	3.81	7900	735,000	2.4	72.0	12.0	14.5	1.0	0.5
February 9, 1931	45 (S)	3.57	7900	632,000	1.1	60.5	23.5	9.5	6.5	
February 15, 1931	52 (S)	4.31								
February 22, 1931	60 (S)	4.87								
March 8, 1931	76 (S)	5.53	7200							

TABLE 7.—CASE 7. CATHERINE MCC.

Date.	Hemo- globin, per cent.	Red blood cells, millions per cu.mm.	White blood cells, per cu.mm.	Reticulo- cytes, per cent.	Neutro- phils, per cent.	Lympho- cytes, per cent.	Mono- cytes, per cent.	Eosino- phils, per cent.	Baso- phils, per cent.
September 11, 1925	75 (T)	4.19	11,500	....	62.0	30.0	4.0	4.0	0.5
May 26, 1930	60 (T)	4.00	7,700	....	74.0	25.0	....	0.5	
August 27, 1930	55 (T)	3.71	6,900	....	73.5	24.0	1.5	1.0	
September 30, 1930	50 (T)	4.21	8,500	....	75.0	20.0	4.0	0.5	
December 31, 1930	45 (T)	4.06	4,650	0.4	65.0	25.0	7.0	3.0	
February 17, 1931	47 (S)	3.80	8,600	0.2	66.5	28.5	3.0	2.0	
February 20, 1931	Iron and ammonium		citrate, 8	gm. daily	begun.				
February 21, 1931	50 (S)	....	....	1.8					
February 23, 1931	....	4.24	4,950	4.4					
February 24, 1931	....	....	....	4.7					
February 25, 1931	....	....	....	7.3					
February 26, 1931	54 (S)	4.24	5,750	3.5					
February 27, 1931	....	....	....	1.7					
February 28, 1931	....	....	....	2.9					
March 2, 1931	55 (S)	4.10	4,800	1.6					
March 5, 1931	61 (S)	3.90	4,900						
March 9, 1931	....	....	....	1.3					
March 10, 1931	67 (S)	4.39	4,800	1.9					
March 12, 1931	68 (S)	4.38	6,700	1.7					
March 16, 1931	72 (S)	4.37	4,700	0.9					
					61.0	34.5	3.5	0.5	0.5
					63.2	30.0	5.6	0.8	0.4

## DAMESHEK: PRIMARY HYPOCHROMIC ANEMIA

showed no occult blood; blood and spinal fluid Wassermann reactions were negative. Gastric analysis showed complete absence of free hydrochloric acid both in the fasting contents and for 1 hour after the injection of 0.6 mg. of histamin in solution. Total acid varied from 20 to 36 units per 100 cc. The rest of the laboratory data are seen in Chart V. The diagnosis of primary hypochromic anemia was made. It was felt that although this may have been aggravated by her recent pregnancy, the anemia was "primary" and probably associated with gastric atrophy and an erythroblastic bone-marrow.

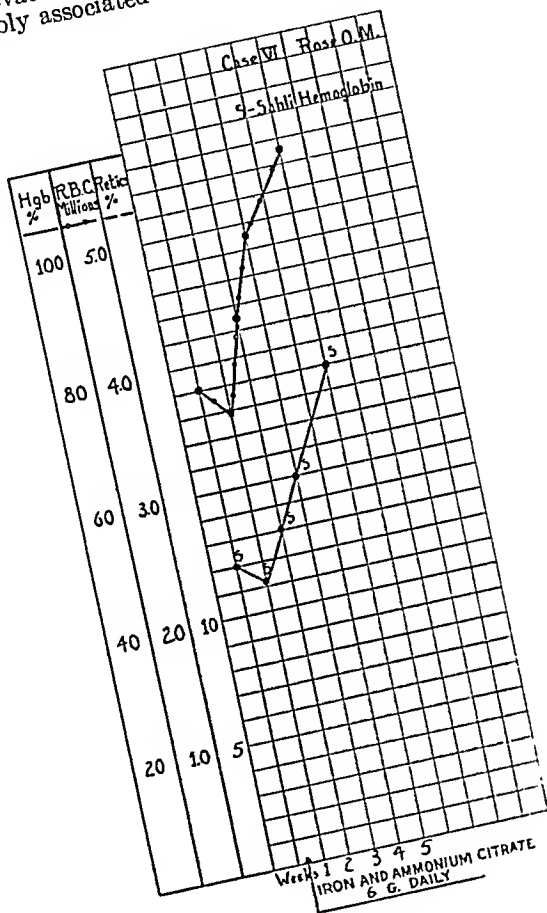


CHART V.

**Clinical Course.** The patient rapidly improved and was entirely free of all mental symptoms within a few hours. On February 8 she was given ferric and ammonium citrate in doses of 6 gm. daily and was discharged from the hospital on February 10 with instructions to continue with that medication and an ordinary diet without liver. On February 15, she felt much better but complained of sharp precordial pain associated with exertion. There was definite rise in hemoglobin and red blood cell count. On February 22, she showed continued improvement and was much stronger. Her appetite was ravenous and she was constantly hungry. A sample of her daily dietary was this: breakfast—grapefruit, apple sauce, 6 slices of toast

plentifully buttered, 1 egg, 2 cups of tea with sugar; morning luncheon—orange, 2 crackers; dinner—4 ounces of broiled steak, 1 potato, 2 green vegetables, 4 slices of buttered bread, jelly, 2 cups of tea; afternoon luncheon—fruit and milk; supper—4 to 5 slices of bread and butter, potatoes, cake and tea; night luncheon—fruit. Hemoglobin and red blood cell count had risen sharply, the color of the hands, face and mucosæ being noticeably improved. She was asked to continue with 6 gm. of iron daily, and there was continued rapid improvement in both hemoglobin and erythrocyte count.

**Summary of Case 6.** A French-Canadian woman, aged 28 years had been pale since childhood. Five months before admission she was delivered of a baby but had remained well until 3 weeks before admission when she suddenly developed some peculiar mental symptoms which were repeated on the morning of admission. The diagnosis of hysteria was made. She was found to have a moderately severe anemia of the hypochromic type associated with complete absence of free hydrochloric acid. There was prompt response to large doses of iron.

**CASE 7.**—Catherine T. McC. (Boston State Hosp. No. 26253).<sup>\*</sup> A single woman, aged 49 years, was committed to the hospital on September 2, 1925, for treatment of an "undiagnosed psychosis, (?) mental deficiency." Family history was irrelevant. At the age of 3, a questionable hydrocephalus was found. She was mentally below par, and, finally developing hallucinations and other mental symptoms, was committed to the Boston State Hospital. Physical examination was essentially negative except for slight pallor and a large head.

In May, 1930, Dr. Tryon noticed that the patient was pale. Blood studies at this time showed a "secondary" type of anemia: hemoglobin, 60 per cent (T); red blood cell count, 4,000,000 per cu.mm. No cause for the anemia could be discovered, although it was felt that it might be associated with menopausal symptoms, *i.e.*: catamenia every 2 to 3 months, and slight menorrhagia. The dietary was the ordinary hospital one, perhaps somewhat deficient in meats, but apparently adequate, since no dietary deficiency could be demonstrated in the other patients. Pills of ferrous carbonate (1 gm. daily) were given, though not regularly, from May, 1930, until February, 1931. Despite this treatment the anemia became progressively worse as may be seen from Chart VI so that on February 18, 1931, hemoglobin was 47 per cent (S) and erythrocyte count 3,800,000 per cu.mm. Gastric analysis, done by Dr. Raskind, disclosed complete absence of free hydrochloric acid after histamin stimulation.

The writer was asked to see the patient on February 19. She was found to be up and about the ward, fairly alert mentally and able to answer questions rationally. She felt well and had no complaints. Physical examination showed a pale, rather obese woman with "pepper-and-salt" hair such as is seen frequently in pernicious anemia. The mucosæ and conjunctivæ were quite pale. There was no icterus. The tongue was completely smooth, being entirely devoid of papillæ, somewhat atrophied and shiny. Reflexes were somewhat exaggerated.

The urine showed traces of sugar from time to time. Stools were negative for occult blood. Icteric index was 4. Blood studies showed a hypochromic anemia, red blood cells being markedly hypochromic and varying widely in size and shape. Average red blood cell diameter was 6.48 micra, cells

<sup>\*</sup> I am enabled to report this case through the courtesy of Dr. Tryon of the medical staff of the Boston State Hospital.

varying from 3.0 to 7.5 micra in size. Forty-seven per cent of the cells were 6.0 micra or less in diameter.

The diagnosis of primary hypochromic anemia was made and the patient started on ferric and ammonium citrate, 8 gm. daily, on February 20, 1931. There was a good reticulocyte response which reached its peak (7.3 per cent) 5 days after treatment was begun. Hemoglobin rose slowly, but erythrocytes lagged. Observations are still being continued on this patient.

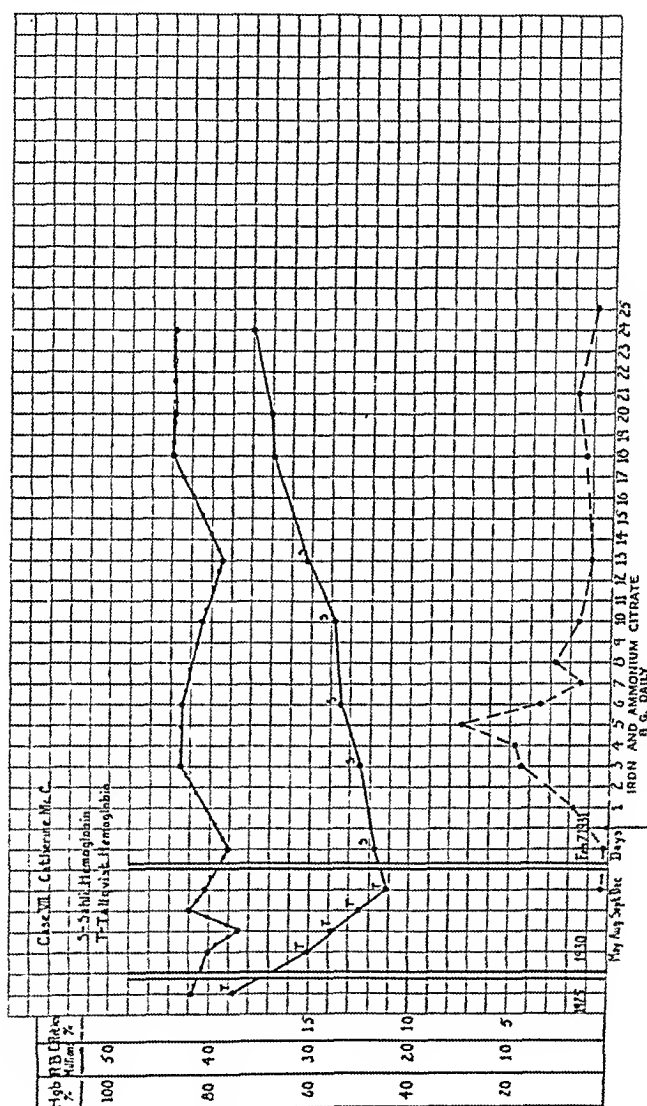


CHART VI.

**Summary of Case 7.** A 49-year-old inmate of a State hospital for the insane was found to have a moderate degree of hypochromic anemia without apparent cause. There was atrophied tongue and achlorhydria. Treatment with iron relieved the anemia.





**Analysis of Cases.** *Sex.* In the 7 cases described here, 6 were females and 1 a male; in 3 cases seen by Young at the Boston Dispensary,\* all were females. All authors who have written on the subject are agreed that the disease is typically seen in women. This has naturally led to the thought that there might be a relationship to chlorosis, in fact a "latter-day" chlorosis. Sepänen,<sup>12</sup> on the basis of 278 adequately studied cases of hypochromic anemia of all types, finds that "simple" anemias are much more common in women than in men.

*Age.* Of the 7 cases studied here, 2 were in the second decade, 3 in the third decade, and 2 in the fourth. The 3 Boston Dispensary cases, ranged in age from 37 to 45. Meulengracht<sup>13</sup> states that these cases ordinarily occur in the fourth decade of life. This is in contradistinction to chlorosis, which, authorities agree, develops typically in girls from 14 to 20 years of age, and is rarely seen after the age of 30.

*Nativity.* The cases of the present series were divided as follows: 1 Canadian-Irish, 2 Americans, 1 Russian-Jew, 1 Scotch, 1 French-Canadian, and 1 Irish-American. Apparently these cases may occur in any nationality. They have been reported from Germany, Canada, the Scandinavian countries, and from this country. Brown eyes and brown hair, said to be uncommon in patients with pernicious anemia, were fully as common in the present series as blue eyes and blonde hair.

**Symptoms.** Ordinarily, onset of symptoms is associated with development of severe anemia with its sequelæ of dyspnea, weakness, and fatigue. Burning tongue, digestive disorders, paresthesias are common, particularly if the anemia is severe, although in Case 4 symptoms referable to the central nervous system were dominant despite the relative mildness of the anemia. The characteristic features in the symptomatology are their chronicity, and the tendency to development of relapses which are ordinarily associated with mild infections, slight bleeding, or fatigue due to increased exertion. When a definite story can be elicited, relapses are found to occur during the fall and winter, remissions during the summer. Headaches and vertigo are common. Dyspnea and palpitation are the rule. Anorexia is common; diarrhea may occur. Menstrual disorders may develop.

*Physical Examination.* Examination discloses pallor of varying degree, a pallor without icterus. The "greenish pallor" said to be characteristic of chlorosis was not seen in the patients of this series except possibly in Case 4 during her third relapse. The tongue is invariably smooth, shiny, frequently reddened and ordinarily without coat. It is typical of the tongue of pernicious anemia. The spleen may at times be felt, but is not usually enlarged. There may be signs of "combined system disease," such as diminished

\* Personal communication to the author.

vibratory sense, diminished knee jerk, positive Babinski, etc. Changes in the finger nails ("spoon" nails, brittle nails) are common.

**Laboratory Data.** 1. *Gastric Analysis.* The gastric juice ordinarily shows either absent or markedly diminished hydrochloric acid. Kaznelson, Reimann, and Weiner<sup>2</sup> found all their cases achylie. The authors who mention this disorder, usually in passing, state that it is a simple anemia associated with achylia. It is interesting to note in this connection that chlorosis was generally associated with hyperchlorhydria. In the 7 cases reported here, 4 (Cases 1, 5, 6, 7) were completely achylic. The others showed some, though usually markedly diminished, secretion. In the 3 cases of Young's at the Boston Dispensary, all showed achylia even after subcutaneous injection of histamin. Achylia is thus usually present, but is not a constant finding.

2. *Icteric Index.* This was found to be low in those cases in which the test was performed. In Cases 1, 3 and 7, the index was 4 (normal 6 to 10). The low index is probably due to the normal amount of blood destruction in the presence of diminution in number of red blood cells.

3. *Blood Findings.* Hemoglobin is reduced to a greater degree than the red blood cell count. The color index is thus below unity and the red cells hypochromic. The lowest readings of hemoglobin and red blood cells were seen in Case 1—hemoglobin 12 per cent (S); and red blood cell count 1,800,000 per cu.mm. Besides the hypochromia, changes in size and shape of red blood cells are quite striking at times. Polychromatophilia and increase in reticulocytes are not ordinarily seen. Normoblasts may at times be seen, especially if the anemia is severe. Red blood cell diameter is much reduced, ranging in these cases from 5.8 to 6.2 micra. Leukopenia (to as low a figure as 2 to 3000 white blood cells per cu.mm.) is the rule, this being due to an absolute reduction in granulocytes. The nuclei of the polymorphonuclear cells are usually many lobed, resembling the "pernicious anemia neutrophil." The lymphocytes are increased in relative number. Monoocytes are ordinarily diminished. Blood platelets are ordinarily diminished during relapse but may be greatly increased during remission. During this phase, there is a rise in reticulocytes, not to so great an extent, to be sure, as in pernicious anemia, but to fairly high levels (9 to 10 per cent). This rise usually occurs within a few days after onset of therapy, at a somewhat shorter interval than in pernicious anemia. Leukocytes may be 10,000 or 12,000 per cu.mm., the increase being due to a marked rise in polymorphonuclear cells. Blood platelets become increased to a striking degree—in 1 case rising from 40,000 to 1,250,000 per cu.mm. Once having become increased, they tend to remain at a high level.

4. *Bone-marrow Biopsy.* Biopsy of the sternal marrow was performed in 3 of the present series of cases, the technique of Seyfarth<sup>14</sup>

being used. Smears and sections were made. The same findings were present in all 3 cases. Despite the severe anemia, the leukopenia, the reduction in thrombocytes—all of which would lead one to suspect some degree of aplasia of the marrow—the bone marrow was crowded with nucleated red cells.\* These were all of the normal erythronormoblastic type, no megaloblasts being seen. Islands of erythroblasts were common. These were composed of fairly large hemoglobin-containing nucleated cells, larger than the normoblast and containing a nucleus composed of blocks of chromatin. Kaznelson, Reimann, and Weiner<sup>2</sup> have described this identical picture in their biopsied cases of the disease. The overabundance of nucleated red cells, the islands of immature hemoglobin-containing cells are reminiscent of the state of the marrow in pernicious anemia, in which, despite the anemia, there is overabundance of nucleated red cells and islands of a special type of immature red cells—the megaloblast.

**Treatment.** One of the most characteristic features of the disease is the prompt and dramatic response to large doses of iron. It has been the experience of all who have written on this subject that the dosage of iron must be large, from 3 to 6 gm. daily. In Central Europe reduced iron has been used. In a large group of patients with hypochromic anemia of all types, the author has used with excellent results the soluble ferric and ammonium citrate in 25 per cent aqueous solution. The dosage has varied from 2 to 8 gm. daily. In these cases of primary hypochromic anemia a dosage of 3 to 6 gm. daily has been found adequate to induce a remission within 3 to 5 days. On the third or fourth day following the induction of treatment with iron, the patient may suddenly develop a sensation of strength and well-being heretofore absent, as well as a desire to eat. The appetite becomes voracious, the soreness of the tongue disappears, paresthesias, if present, diminish, and there is marked gain in weight. This is well brought out in Cases 1, 2 and 6 of this series. Coincident with the onset of these symptoms, there is a rise in reticulocytes which has been discussed above. The suddenness of onset of remission, the voracious appetite which develops, are strikingly reminiscent of the effect of liver extract in patients with pernicious anemia. As with liver in the latter disease, the dosage of iron in primary hypochromic anemia must be adequate. Thus in Case 1, there was a cessation of rise in hemoglobin red blood cell count on 3 gm. of iron daily, but with 6 gm. daily, there was again a prompt response. If the iron is discontinued, a relapse may occur (Cases 1, 2, 3). These considerations are suggestive of a deficiency in iron. It is probably advisable, therefore, when normal hemoglobin and red blood cell counts have been obtained, to main-

\* It has been conclusively shown by Custer and others that the marrow of different bones will show widely different pictures in a given case. The sternal marrow is notoriously one of the last to become hypoplastic.—EDITOR'S NOTE.

tain the patient on a relatively small dose (1 gm.) of iron daily.\* Table 8 presents in tabular form the symptoms, signs, and laboratory data noted in the cases presented in this paper.

**Discussion.** As noted in the introduction, it seems difficult, so firmly has the idea become ingrained, to conceive of a primary anemia with the so-called "secondary anemia"—hypochromic, microcytic—type of blood picture. The entire classification of the anemias is at the present writing in a state of confusion: pernicious anemia no longer has its pernicious outlook; we see no more of the "green sickness" chlorosis. It would be advisable, to be sure, to classify the anemias on purely etiologic grounds, but this ideal is as yet far from attainment. Some of the proposed classifications, each emphasizing a different angle of the problem, are as follows: (1a) *primary* (cause not known) and (1b) *secondary* (cause known); (2a) *essential* (in which the anemia is the dominating symptom): chlorosis, pernicious anemia, aplastic anemia, familial hemolytic jaundice and (2b) *secondary* (in which the anemia is a phenomenon secondary to a separate disease entity); (3a) *hyperchromic* (in which there is anemia and yet the red blood cell has its full complement of hemoglobin) and (3b) *hypochromic* (in which the red blood cell is insufficiently filled with hemoglobin); (4a) *macrocytic* (in which the average red cell diameter is above the normal of 7.5 to 7.8 micra) and (4b) *microcytic* (the average red blood cell diameter below 7 micra); (5a) anemias due to *faulty blood formation* (pernicious anemia, chlorosis, aplastic anemia) and (5b) *increased blood destruction*, etc. In spite of all these attempts to classify the anemias on purely hematologic or physiologic grounds, the old descriptive names of pernicious anemia, chlorosis, familial jaundice have persisted in current usage. Until the ideal classification based on etiology is attainable it might be advisable to classify the anemias on purely histopathologic grounds. Thus pernicious anemia would be megaloblastic anemia; the name aplastic anemia would stand; the anemia here discussed would be erythronormoblastic anemia; the anemia of familial jaundice might be reticuloendothelial or macrophagic anemia. It is true that the histopathology of the bone marrow has not as yet been sufficiently studied to permit any clear-cut descriptions of all the anemias, but with the increasing use of the bone-marrow biopsy as a diagnostic procedure, this might be possible. It is to be remembered in this connection that such an admittedly temporary descriptive classification is widely used for tumors where again the etiology is unknown.

The megaloblastic (hyperchromic, macrocytic) anemia called "pernicious" has been shown by the researches of Castle<sup>8</sup> to be a virtual deficiency disease due to inadequate protein digestion in a peculiarly diseased stomach. However, the cause for the gastric

\* Since writing this paper, further data on the effects of various substances on the anemia have been obtained. It is planned to incorporate these data in another article.

atrophy has not as yet been found; nor has it been determined why these individuals develop an embryonic megaloblastic reaction rather than the ordinary erythronormoblastic response; again the cause of spontaneous remissions has not been elucidated. The megaloblastic marrow has brought up the idea of a constitutional factor—well borne out in certain pernicious anemia families. At any rate there is now no question that gastric digestion in pernicious anemia is at fault. This is seen to be due to gastric atrophy which in turn may be occasioned by unknown factors or may be congenital, syphilitic, infectious, or the result of pregnancy.<sup>15</sup> Various authors have concluded that pernicious anemia is a symptom complex due to diverse causes associated with a constitutional factor: a megaloblastic bone-marrow. This highly unusual marrow is, in the final analysis the only pathognomonic sign of the disease—the symptomatology of jaundice, macrocytosis, hyperchromia, smooth tongue, nervous system signs, gastric anacidity, even response to liver therapy being possible in other conditions. It may well be, therefore, that (1) given an embryonic rest of megaloblasts in the bone marrow, an individual with (2) gastric atrophy may, with (3) a stimulus, such as infection, pregnancy or fish tapeworm, develop the anemia ordinarily spoken of as pernicious. It is possible, however, that every individual (regardless of embryonic rests or constitutional types) who has the type of gastric atrophy found in pernicious anemia will in the course of time develop the peculiar bone-marrow picture which is found in pernicious anemia. This concept is certainly difficult of proof.

The group of cases presented in this paper parallels very closely a group of cases of pernicious anemia; at times the resemblance is indeed striking. Thus in Case 1 we see a history of remissions and relapses, sore tongue, paresthesias, diarrhea, a smooth tongue, absence of hydrochloric acid after histamin, neurologic signs, leukopenia, thrombocytopenia—in fact all the symptoms and signs of pernicious anemia except the hyperchromia, the macrocytosis, and the elevated icteric index. In the final analysis, the only difference between the 2 types of cases is that in pernicious anemia the marrow is crowded with megaloblasts which, if not embryonic, are certainly not normal; whereas in the other type, one sees an erythronormoblastosis: a crowding of the marrow with smaller, more normal cells. In both types there appears to be a defect in maturation, for despite the marked hyperplasia of nucleated red cells there is in both instances a marked anemia. The defect in maturation in the first type has been shown by Castle<sup>8</sup> to be due to a virtual deficiency in a certain protein subsequent to impaired gastric digestion. Most of the cases presented here are deficient in free hydrochloric acid which hints at some gastric disturbance. The accompanying glossitis is also evidence in this direction. The defective gastric digestion may lead to an inadequate digestion of organic

iron, thus permitting (to paraphrase Castle<sup>8</sup>) the development of a virtual deficiency in the presence of a diet adequate for the normal individual. This defective maturation of red cells may be remedied in the first instance by sufficient dosage of liver extract, properly digested protein or gastric extract; and in the second instance by inorganic iron in sufficient dosage. Whether disturbed protein digestion alone brings about a megaloblastosis or whether an embryonic rest of megaloblasts is also necessary is not yet clear. In this connection, one may speculate that an individual with a megaloblastic marrow will develop under certain conditions the ordinary pernicious anemia, whereas one with a normal marrow will under the same conditions develop the type of anemia presented here.

Apropos of this, the interesting observation has been made by Faber and Gram<sup>6</sup> of a family in which there were 3 patients with achylia gastrica; 2 of them, father and son, died of pernicious anemia, the third, a daughter showed a pronounced "relapsing microcytic type of anemia." The latter patient ("curiously enough," the authors note) showed a typical glossitis.

More extended observations on this unusual family have recently been made by Gram.<sup>16</sup> He has been able to study 3 generations. The father and his 2 eldest sons died of typical pernicious anemia. A daughter, aged 43, in 1919 had achylia gastrica, glossitis, and a microcytic anemia relieved by iron. In 1928, she had a "latent" pernicious anemia blood picture, and in 1929 full-blown pernicious anemia. Another daughter of 47 also had a pronounced microcytic anemia associated with achylia and responding to iron. Of 10 grandchildren, most had marked hyperacidity and gastric hypersecretion, interpreted as possible gastritis. Gram felt, on the basis of these observations, that pernicious anemia was dependent on an hereditary factor and that it might pass through these phases: acid gastritis, slight temporary "simple" anemia, dyspepsia, glossitis, achylia, severe temporary "simple" anemia, and finally pernicious anemia. Other authors have noted the occurrence of a "simple" anemia in members of a family in which pernicious anemia is present.

Faber<sup>6</sup> in 1913 first pointed out that an anemia of some type was found in 28.5 per cent of 207 patients with achylia. In 1924, the same author<sup>6</sup> found anemia (usually hypochromic or "simple") in 41 per cent of all cases with achylia. Kaznelson, Reimann, and Weiner<sup>2</sup> also have observed 25 cases identical with the ones described here; they discuss gastric achylia as an etiologic factor.

McLester,<sup>17</sup> in a recent article on "Clinical Syndromes that Include Achlorhydria," reports a few cases with the typical symptomatology of pernicious anemia, sore tongue, and achlorhydria. His Cases 1, 2, 3, and 7 resemble the ones described here. In Case 2, McLester makes the interesting observation that he is "inclined, in spite of failure to find typical blood changes, to regard her disease as pernicious anemia." He states that the "difficulty of categorically

labeling these patients illustrates the possible kinship between the diseases of this group." Christian,<sup>18</sup> in an article on "The Achlorhydria Family Tree of Diseases" made somewhat similar observations.

The reasoning, which takes into account "embryonic rests," etc.,<sup>19</sup> is speculative, and somewhat impaired by the experiments of Castle.<sup>8</sup> In one of these, protein incubated with the gastric juice of 2 cases of "chronic chlorosis" was active in causing a remission in pernicious anemia. The reverse was apparently not tried. Further experimentation on these points is advisable. The observations in Gram's<sup>16</sup> family of pernicious anemia, particularly on the patient who passed through the stages of microcytic anemia, latent pernicious anemia, and full-blown pernicious anemia, are interesting in this connection. I have recently observed at the Beth Israel Hospital another instance of this transition from a hypochromic anemia responding to iron to a hyperchromic anemia typically "pernicious" responding to liver. From the above speculations and with the cases presented here in mind, the possibility presents itself that "pernicious" anemia may be of 2 types: the ordinary megaloblastic (macrocytic, hyperchromic) and the unusual (or but little known) erythroblastic (microcytic, hypochromic) anemia.

What relationship has primary anemia of the erythroblastic, hypochromic type to another disease called chlorosis? This disease, a primary or essential anemia occurring in women and characterized by an extremely low color index, is universally considered to be at the present time almost defunct. One of the mysteries of medicine is how a disease so common in 1880 and 1890, should in 1930 have become so rare that one never sees an example of it. It is possible, to be sure, that the diagnosis of chlorosis was being made so commonly during the last century, that any girl or young woman who was slightly pale and who complained of fatigue, weakness, vertigo, and menstrual disturbances was considered to be chlorotic. At the present time, the tendency may be to call these cases "neurosis" and the accompanying anemia (always of the hypochromic type) "secondary." Can it be that the cases described here are not really instances of a "new" type of idiopathic anemia, but rather examples of chlorosis? Mills,<sup>4</sup> in discussing "idiopathic hypochromic anemias" speaks of "present-day chlorosis," in which the hemoglobin is reduced, although the red blood cell count is normal, as are the counts of the white blood cells and blood platelets. He says that free hydrochloric acid is not infrequently absent from the gastric juice and that response to Bland's pills is rare; he recommends highly ultra-violet ray therapy. Schulten<sup>3</sup> also speaks of this latter-day chlorosis ("spät-chlorose") which responds to large doses of iron. In discussing the relationship between gastric achylia and "simple" anemia, Faber and Gram<sup>6</sup> state that although this anemia may resemble chlorosis, it differs from it by its presence in

both sexes and by its tendency to recur. Kaznelson, Reimann, and Weiner<sup>2</sup> call the disease "achylic chloranemia" (achylische chloranämie). According to various treatises on chlorosis,<sup>21</sup> the disease is characterized by very slight, if any reduction in red blood cells and by a hyperchlorhydria in the large majority of instances. It usually develops at puberty, may recur up to the age of 30, but tends to disappear before that age, especially if marriage or pregnancy (or both) have supervened. It is said never to begin after the age of 27. Sore tongue and symptoms of combined system disease are never mentioned.

Let us examine critically the case presented here with regard to chlorosis.

CASE 1. A married woman, aged 44 years, disease of five years' duration; hemoglobin, 12 per cent; red blood cell count, 1,900,000 per cu. mm.; white blood cell count, 3200 per cu.mm.; achlorhydria; central nervous system manifestations. All of these manifestations, the age group, the severity of the anemia appear to rule out chlorosis.

CASE 2. A man, aged 37 years. The sex alone rules out the disease, although certain authors report cases of chlorosis occurring in men. This is held to be impossible by most authorities. The age is wrong for chlorosis.

CASE 3. The marked anemia associated with leukopenia and thrombocytopenia, the low gastric acidity, all appear to rule out the disease. It is possible, however, that this case might have been called chlorosis in the last century.

CASE 4. The age, sore tongue, almost complete absence of free hydrochloric acid from the stomach, the neurologic symptoms would rule out chlorosis according to the authorities consulted.

CASE 5. The age, sore tongue, absence of free hydrochloric acid from the stomach here again tend to rule out chlorosis.

CASE 6. The peculiar symptomatology, the absence of free hydrochloric acid from the stomach appear to rule out chlorosis.

CASE 7. The age, the gastric anacidity again appear to rule out chlorosis.

To summarize, the last 4 cases, being relatively mild, suggest chlorosis but are probably ruled out by the age groups, the lingual manifestations, the tendency to diminution or absence of free hydrochloric acid, and central nervous system symptoms. The first 3 cases are too severe to be classed as chlorosis. After all, when we discuss chlorosis, we are speaking of what is to us of the present medical generation an indefinite disease with a peculiar name and an unknown pathology. Until we know more of the pathology and pathologic physiology of that disease, it seems wise at present to drop the term chlorosis. If the instances of so-called chlorosis are intensively studied with present-day methods, it is possible that they will all be placed in the group under discussion here.



The cases described here, then, present a symptomatology which is strikingly like that of pernicious anemia. The objective phenomena of pallor, smooth tongue, central nervous system manifestations, and achlorhydria resemble pernicious anemia; the blood findings of achromia and microcytosis at first glance seem to rule out pernicious anemia, but when one considers that the marrow in both cases is hyperplastic—in pernicious anemia megaloblastic, in these cases erythronormoblastic—and the immature nucleated red cells ready to mature if given the proper stimulus, the blood picture becomes rather subsidiary to a broader conception of the disease. There is possible relationship of this group of cases to chlorosis, but in view of such factors as age group, sore tongue, achlorhydria, etc., this relationship seems to be minimized.

**Summary and Conclusions.** Seven cases of an anemia are described in which, although the symptomatology was that of pernicious anemia, the hematologic findings were those of a "secondary" anemia. Most of these cases gave a history of remissions and relapses of anemia, sore tongue, gastro-intestinal symptoms, and parasthesias. Objectively, they showed pallor without icterus, atrophied tongue, "spoon" nails and, at times, signs of "combined system disease." All known causes for a secondary anemia were absent. Achlorhydria or hypochlorhydria was present. The blood picture showed low color index, hypochromia, low average red blood cell diameter, leukopenia, relative lymphocytosis and thrombocytopenia. Sternal bone-marrow biopsies in 3 cases disclosed, despite the severe anemia, marked hyperplasia due to crowding with erythroblasts and normoblasts. The anemia and all of the symptoms responded promptly to large doses of inorganic iron, but there was a tendency to relapse when iron was discontinued.

The relationship of this anemia to the megaloblastic hyperchromic anemia called "pernicious" is discussed in detail. Pernicious anemia shows pathologically a hyperplastic marrow crowded with abnormal or embryonic nucleated red cells called megaloblasts which apparently mature very inefficiently unless liver or stomach or normally digested protein is given. The erythroblastic hypochromic anemia described here shows pathologically a hyperplastic (sternal) marrow crowded with the more normal erythro- and normoblasts which apparently mature very inefficiently unless inorganic iron is given in large doses. This anemia may be due to a virtual deficiency subsequent to inadequate digestion of organic iron.

The possibility that the cases described here are instances of chlorosis is discussed and rejected.

It is felt (1) that the hypochromic anemia described here is "primary" or "essential;" (2) that it is related to pernicious anemia of which it may be an unusual type; (3) that it is probably dependent upon an inadequate gastric digestion of organic iron which may

thus lead to faulty hemoglobin synthesis and improper maturation of erythro- and normoblasts in the bone marrow.

NOTE.—Since this paper was written 5 other cases closely similar to those cited have been observed.

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## IDIOPATHIC HYPOCHROMEMIA.

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In a preliminary paper<sup>1</sup> published in February, 1930, the author reported a series of 10 cases of anemia, all in women, and characterized by a chronic prolonged course, a "secondary" type of blood picture, a tendency to resist ordinary anemia therapy, and almost invariably by the absence of free hydrochloric acid from the gastric contents. It was further shown that these cases, unusually resistant to ordinary therapy, could be greatly benefited by adding small amounts of copper salt to Bland's mass. The term idiopathic hypochromic anemia was suggested for this disease.

The conviction that such cases represented a disease entity separate and distinct from chlorosis and postpartum anemia (Osler<sup>16</sup>), with which the condition has certain features in common, appears to have originated simultaneously in this country<sup>2</sup> and in Germany.<sup>3</sup> Isolated instances of "secondary" anemia of undetermined etiology have been reported for many years. Faber's paper<sup>4</sup> in 1913 contains the first clear-cut description of the disease. Since this time similar cases have been reported by Weiner and Kaznelson<sup>5</sup> (1926), Spenson<sup>6</sup> (1926) and Altschuller<sup>7</sup> (1929) and others. Although brief reference to simple anemia with achylia was made by Lee and Minot<sup>8</sup> in 1928, the first adequate descriptions of the disease appeared the following year.<sup>2,3</sup>

**Nomenclature.** At the present time there appears to be no unanimity of opinion as to the most suitable nomenclature for the disease. Weiner and Kaznelson,<sup>5</sup> who probably deserve credit for attempting to establish the disease as a clinical entity, referred to the 3 cases which they published in 1926 as "cryptogenic achylic chloranemia." In their later and larger series of cases<sup>3</sup> they employ the term achylic chloranemia. Watkins<sup>2</sup> uses the rather paradoxical title "idiopathic secondary anemia." Mills suggested the term idiopathic hypochromic anemia to overcome the word "secondary," which refers only to the type of blood picture. The use of hypochromic to describe these cases has been accepted independently by Schulten<sup>9</sup> and by Waugh.<sup>10</sup> More recently Mettier and Minot<sup>11</sup> (1931) have referred to such cases as chronic chlorosis, though this term would appear to be inappropriate as the disease differs from chlorosis in that hyperchlorhydria, not achlorhydria, is a feature of the latter.

In our opinion the choice of a name for the disease lies between achylic chloranemia and idiopathic hypochromic anemia or hypochromemia. The latter is preferred because occasionally a case is

encountered with a small amount of free hydrochloric acid in the gastric contents and which cannot be otherwise distinguished from typical instances of the disease. Witts<sup>12</sup> suggestion "simple achlorhydric anemia" is open to the same criticism.

**Incidence of the Disease.** An accurate determination of the incidence of idiopathic hypochromemia is not easily obtained in a medical outpatient clinic where cases are not classified according to disease. In 1929 10 cases were recognized in the medical outpatient department of the Montreal General Hospital, and in 1930 10 new cases out of a total of 6863 medical admissions, though the true incidence of the disease is probably much greater. Nevertheless, Witts was able to collect only 50 cases at Guy's Hospital by analyzing the records from 1922 to 1929. Seppänen<sup>13</sup> has recently investigated 209 cases of hypochromic anemia. Fifty-five were due to hemorrhage, 61 to infections, 33 to malignant tumors and 19, or 10 per cent, were of the idiopathic type. It is of interest that all the idiopathic cases were females whereas the other types were evenly divided between the sexes.

**Predisposing Factors.** (a) *Age and Sex.* All of our cases have been women despite a diligent search for instances of the disease among the male sex. Only one instance of the disease in the male has been recorded in the literature.<sup>12</sup> The disease shows a marked predilection for the fourth decade. Fifteen of 23 cases, or 65 per cent, occurred between the two ages of 30 and 40 years, usually toward the end of this age period. The youngest case was a girl aged 26 and the eldest a woman aged 61 years.

(b) *Occupation.* Overwork, poor hygienic conditions and improper food appear to play a minor rôle in the etiology. A lot has been written about nutritional anemia and the militating influence of overwork and unhealthy surroundings upon anemia. No doubt such circumstances are important, but they are not intimately concerned in the pathogenesis. Four of the cases in this series lived in ideal surroundings and had an abundant and well-balanced diet. In but one instance could dietary influences be blamed for the anemia and in this case the response to iron and copper therapy was rapid and complete in spite of the same home conditions.

(c) *The Influence of Pregnancy.* At first sight pregnancy would seem to play an important rôle in the pathogenesis of the disease. Three cases gave a history of a number of pregnancies rapidly succeeding each other with the development of anemia during 1 or more of these, and 5 others first noticed symptoms following labor or miscarriage. A brief résumé of 2 of the cases will serve to illustrate what is true of all cases, namely, that the pregnancy is a complication rather than an etiologic factor in the disease.

CASE 1. Mrs. L., 7833-29, aged 38 years, is the mother of 3 children. She first became anemic following the birth of her second child, now 12 years of age, and at that time was treated with partial success. Ever since

this time she has been pale and has had fatigue and dyspnea on mild exertion. Toward the end of 1928 she became worse, having syncopal attacks and paresthesia of the fingers and toes. In June, 1929, when her hemoglobin was 60 per cent, she was placed on a mixture of iron and copper. In September, 1930, the hemoglobin was 84 per cent. She returned in October, pregnant and since this time her symptoms have gradually returned. On December 24 the hemoglobin was only 55 per cent.

CASE 2. The second case is a young woman aged thirty-two years, the wife of a dentist, who has been married 8 years and has been sterile. She had "always been pale and anemic" and had been treated with various iron preparations for some years. She took liver and liver extract for 3 months without improvement. Under iron-copper therapy the hemoglobin rose from 40 per cent to 80 per cent with disappearance of her symptoms and waxy color. A year later she became pregnant, following which her pallor temporarily reappeared.

Obviously pregnancy is not the cause of the anemia in these cases, but the added burden which reduces the hemoglobin level to a point incompatible with the pursuit of the ordinary duties of life. Other cases have shown similar relapses after focal infection.

(d) *Heredity*. Only 1 case of the series gave a family history of anemia, but 1 woman brought her daughter, aged 14 years, to the clinic where the child was found to be decidedly chlorotic.

*Achlorhydria*. An important factor common to all cases was the marked reduction or complete absence of free hydrochloric acid from the gastric contents after the Ewald test breakfast. In this series of 23 cases, 19 had achlorhydria, 2 had low free hydrochloric acid at one period during the fractional meal and 2 were not tested. The response to histamin was not tried. The subsequent course in the 2 untested cases and their response to treatment seems to justify their inclusion in this group. In Witts' series,<sup>12</sup> 44 cases had achlorhydria while 6 cases had some free hydrochloric acid in one fraction.

For a long time achlorhydria has been suspected to be intimately associated with the underlying cause or causes of idiopathic types of anemia. Faber and Gram's<sup>14</sup> careful study on a series of 90 cases of achylia showed 41 per cent to be anemic, the majority of the "secondary" type. It may, therefore, be taken as proved that achlorhydria or achylia predisposes to the production of anemia of the idiopathic type, though this defect is not the cause of the disease. Mettier and Minot's<sup>11</sup> recent observations indicate that the response of anemias characterized chiefly by hemoglobin deficiency to iron therapy is much enhanced when the iron is given in an acid medium. They suggest that achylia results in a change in the hydrogen-ion concentration of the intestinal contents unfavorable to the absorption of iron. It would seem, however, that the acidity or, rather, the alkalinity of the intestinal contents, where iron is actually absorbed, would not be greatly influenced by the degree of acidity of the stomach contents, since neutralization is rapidly effected in the duodenum. Whatever may be the secretory defects associated with achylia it seems certain that the individual with a deficiency

TABLE 1.—ANALYSIS OF CASES.

Case No.	Name.	Age.	Nationality.	Duration of anemia.	Pregnancies.	Paresthesia.	Cord changes.	Spleen.	Glossitis.	Gastric con- dents.	Blood picture.								Complications.	Results of treatment.		
											R. B. C.	W. B. C.	Hb.	Van den Bergh.	Platelets.	R. B. C. diam.	Polys.	Lymphs.			Eosins.	Monos.
1	N. E. (601-29)	40	Irish	"Always"	0	0	0	P	0	0/18	3.6	5,200	30	0	257,000	7.3	55	45	..	..	Infected finger	Good
2	J. C. (2351-30)	36	Can.	1 year	0	P	0	0	0	0/?	3.9	3,000	49	0	409,000	7.6	60	34	6	3	Myxedema	Good
3	O. J. (18155-25)	31	Can.	5 years	5	P	0	0	0	0/?	4.3	7,200	55	0	....	7.8	70	26	1	..	None	Good
4	F. M. (10545-29)	36	Can.	1 year	0	P	0	0	0	0/12	4.5	6,000	50	0	....	7.6	70	30	..	..	None	Good
5	E. M. (3247-26)	41	Eng.	2 years	0	P	0	0	0	0/11	3.7	9,150	70	0	...	7.9	79	17	1	..	None	Good
6	P. L. (4042-27)	39	Scot.	4 year	0	P	0	0	0	0/14	3.7	4,950	38	0	335,000	..	66	33	1	..	Chr. ulcer. colitis	Fair
7	C. M. (5755-29)	58	Scot.	7 years	0	0	0	0	0	0/12	4.3	3,700	48	0	..	7.3	61	32	3	2	None	Good
8	H. F. (4202-29)	26	Can.	10 years	0	0	0	0	0	0/10	3.0	3,300	42	0	375,000	7.0	64	33	..	..	None	Good
9	R. S. (6737-30)	40	Scot.	4 years	0	0	0	0	0	0/7	4.5	8,700	41	0	205,000	7.2	63	33	..	..	Chronic cholecystitis	Good
10	R. C. (14256-29)	39	Scot.	1 year	2	0	0	0	0	0/27	3.9	5,800	58	0	275,000	7.9	58	40	1	1	None	Good
11	J. Mc. (1864-25)	34	Scot.	5 years	0	P	0	0	0	0/0	3.1	7,500	45	0	283,000	7.8	58	40	..	2	None	Poor
12	J. W. (1095-25)	42	Eng.	7 years	1	P	0	0	0	0/15	4.6	5,500	53	0	180,000	7.7	72	22	2	2	None	Poor
13	J. H. (5227-23)	35	Can.	1½ years	3	P	0	0	0	0/35	4.3	4,400	56	0	333,000	7.7	55	43	1	1	None	Good
14	W. L. (7833-29)	38	Eng.	1 year	0	P	0	0	0	0/10	4.2	6,000	60	0	215,000	7.4	68	32	1	1	None	Poor
15	J. H. (5227-23)	35	Eng.	"Years"	0	P	0	0	0	0/35	4.3	4,450	56	0	..	7.9	55	43	1	1	None	Good
16	P. C.	45	Can.	2 years	0	P	0	0	0	?	4.0	5,400	61	0	162,000	7.3	62	36	3	3	None	Good
17	J. Y.	61	Eng.	"Years"	0	P	0	0	0	?	3.1	9,700	30	0	510,000	7.6	66	26	3	1	None	Good
18	R. A. (7182-30)	35	Eng.	2 years	6	0	0	P	0	8/45	3.9	5,400	38	0	150,000	7.4	61	39	..	..	Birth trauma	Good
19	T. W.	46	Scot.	4 years	0	0	0	0	0	0/5	4.6	8,200	47	0	213,000	7.6	..	..	..	..	None	Good
20	A. W. (16564-30)	32	Can.	1½ years	2	0	0	0	0	0/18	2.8	5,500	36	0	..	..	66	28	..	..	None	Good
21	W. M. (13846-28)	47	Eng.	"Years"	0	0	0	0	0	0/12	3.9	5,650	68	0	300,000	7.7	43	63	3	1	None	Untraced
22	O. C. (2336-26)	37	Can.	1 year	5	0	0	P	0	14/33	3.7	4,950	47	0	255,000	7.3	52	45	1	2	None	Good
23	C. G.	32	Can.	"Years"	0	0	0	0	0	0/20	3.7	5,900	40	0	..	..	..	..	..	..	None	Good

or absence of free hydrochloric acid in his gastric contents is even more likely to develop a hemoglobin deficiency anemia than he is to develop anemia of the Addisonian type. In Faber's<sup>4</sup> series of 207 cases of achylia gastrica, 59 patients were anemic, and of these 22 were of the Addison type while the remaining 37 were of the secondary type, a proportion of almost 1 to 2.

*Symptomatology.* The symptoms of the disease are essentially those of any severe form of anemia—namely weakness, lassitude and fatigue on mild exertion. The onset of this train of symptoms was invariably so insidious that the patient was unable to state just when she was last perfectly well. Many claimed to have been anemic all their lives and gave a history of frequent recourse to the family physician for iron tonics, usually without benefit. Of the 20 cases in this series 15, or 75 per cent, sought treatment for symptoms of anemia. Two came to the hospital as a result of minor accidents, and 1 case because of an acute cholecystitis, though she had been anemic for four years prior to her intercurrent illness. Another case came to the eye clinic because of a large retinal hemorrhage causing blindness, but had been under treatment for anemia for "years." Five of the cases with a history of anemia of two or more years' duration first noticed symptoms during the postpartum state though there had been no excess bleeding or infection. Many of the cases gave a history of menstrual disorders, often characterized by excessive bleeding for which no local cause could be found. The train of gastric symptoms usually met with where free hydrochloric acid is absent from the stomach secretion, was lacking in many instances. Several cases admitted to flatulence when questioned, but bouts of diarrhea were not encountered.

The patients were not as a rule undernourished, the average weight of 16 patients being 121 pounds. A gain in weight invariably followed successful therapy.

*Physical Signs.* All patients in the series were women who presented a waxy, bloodless appearance. The sclerotics were pearly white rather than subicteroid in color, and the mucous membranes pallid. In 5 cases the subicteroid appearance of the skin and the well-preserved adipose tissue was such as to suggest pernicious anemia. This appearance is apparently due to the pallor of the skin and the yellow fatty tissue beneath it for none of the cases had any excess of bilirubin in the blood. Examination as a rule revealed no evidence of parenchymatous disease. A systolic heart murmur was present in 9 cases, but without other evidence of cardiac disease. Subacute combined sclerosis of the cord was not demonstrated in any of the cases by the usual methods of examination including pallesthesia and 2 point discrimination tests, though numbness and tingling of the extremities was not an uncommon symptom, occurring in 12 cases.

The spleen was palpable in only 3 cases, reaching just to the costal

margin. In a fourth case it was enlarged to percussion but was not felt. However, in none of these cases was there any increase in the bilirubin content of the plasma or in the urobilinogen in the urine, and this held for the remainder of the series in which no splenomegaly occurred. Glossitis was not observed in any of the cases, though the tongue was frequently described as atrophic at tip and edges. Because of a decided lack of unanimity in opinion concerning atrophy of the tongue in many of the cases the incidence of this sign is problematical. Certainly the glazed tongue of Addison's anemia is seldom seen, though some degree of atrophy is not uncommon.

*The Blood.* The blood picture in the disease is chiefly remarkable for the marked reduction in the hemoglobin level, without a corresponding fall in the number of erythrocytes. Color indices in the vicinity of 0.5 or 0.6 were commonly observed. One of the most striking facts noted in cases which have been under observation from long periods as from 5 to 7 years was the tendency of the hemoglobin level to remain in the vicinity of 50 per cent, neither improving nor dropping lower unless unfavorably influenced by some complication as pregnancy, menorrhagia, hemorrhoids, etc. This same observation has also been made by Waugh.<sup>10</sup>

The reduction in the erythrocytes was never in proportion to the hemoglobin deficiency. Counts under  $3\frac{1}{2}$  millions were seldom encountered, and a majority were in the vicinity of 4 millions (see chart). The platelets were, as a rule, slightly below the normal level but in 2 instances were increased. The leukocytes were nearly always somewhat reduced though normal counts or even slight leukocyte increase was occasionally observed. The differential count of leukocytes showed that the leukopenia was at the expense of the polynuclear cells. In other words there was a relative lymphocytosis. The actual figures may be obtained by referring to the chart.

Evidence of increased hemolysis has not been noted in any of the cases. The bilirubin content of the plasma as determined by van den Bergh tests was always within normal limits. The erythrocytes always averaged slightly below the normal in size, the mean red cell diameter in 19 cases being 7.5 micra as compared with less than 6.5 micra in Dameshek's cases. While scarcely below normal figures for dried cells, this is distinctly less than the average obtained with wet preparations. Variations in size and shape were not remarkable. Stippling and other signs of immaturity as nucleated forms and reticulocytes were not observed.

The cardinal defect in the blood is therefore a deficiency in hemoglobin whether as a result of iron deficiency or failure of utilization has not been determined.

**Diagnosis.** The diagnosis of idiopathic hypochromemia depends primarily upon the exclusion of possible etiologic factors as chronic



blood loss from peptic ulcer or uterine polypi, tuberculosis, syphilis and other chronic diseases capable of giving rise to a severe secondary anemia. Having ruled out possible causes for anemia, and demonstrated a deficiency or absence of free hydrochloric acid in the gastric contents and the existence of a chlorotic blood picture, the diagnosis of the disease is justified.

At this point there naturally arises a criticism of certain of the cases included in this series as those complicated by colitis, myxedema or chronic cholecystitis. May not the anemia have been a complication of these diseases rather than a primary blood disorder? In the first place achlorhydria is uncommon in these disorders and, second, the time of onset of the anemia was clearly long in advance of the complicating factor. In the case of the patient with chronic cholecystitis the anemia antedated the hepatic symptoms by 4 years. The case with myxedema was allowed to return to a state of hypothyroidism but her hemoglobin showed no tendency to revert to its former low level. The fact is that many women with achlorhydria tend to develop anemia of the hypochromic type. Poor hygienic surroundings, defective diet or such diseases as just discussed act as an additional drain upon the hematopoietic tissues aggravating the state of anemia, or, what is much more likely (and this is borne out by the histories) bring about such a reduction in the hemoglobin level as to seriously incapacitate the patient and drive her to seek treatment. However, the majority of patients develop anemia without any complicating factor and consult the physician because of the symptoms to which it may give rise. In either case the condition is essentially a primary blood dyscrasia.

**Differential Diagnosis.** *Pernicious Anemia.* Seven of the cases in this series were referred to the clinic as pernicious anemia. The history of paresthesia, the pallor, the achlorhydria and the absence of any cause for the anemia led to the diagnosis of Addisonian anemia in spite of a hypochromic rather than a hyperchromic type of blood picture. The small type of erythrocytes, the absence of bilirubinemia and the complete failure of liver and liver extract were features which separated these cases sharply from the category of pernicious anemia.

*Chlorosis.* The disease in some respects resembles chlorosis. It is almost always observed in the female sex and the cardinal defect is one of hemoglobin production. On the other hand it affects older women, it runs a very chronic course, and it is unaffected by amounts of iron which rapidly cure chlorosis. Then again hyperchlorhydria is the rule in chlorosis.

*Splenic Anemia.* In our experience, difficulty has been encountered in ruling out instances of early splenic anemia. One patient, Mrs. W., aged 37 years, with a history of anemia of 3 years' duration, achlorhydria and a nonpalpable spleen failed to improve on treatment. A year later the spleen became palpable and bilirubinemia

and urobilinuria made their appearance. A feature which from the beginning should have raised the question of early splenic anemia was the persistent leukopenia of from 1000 to 3000 leukocytes per c.mm.

*Acute Hemolytic Infectious Anemia.* Idiopathic hypochromemia may be confused with acute infectious anemia. A series of cases of this disease has recently been reported by Lederer,<sup>15</sup> and 2 cases have come under our observation. The acuteness of the onset, the pyrexia, the bilirubinemia and urobilinuria of acute infectious anemia are the differential points as actual blood pictures may not present marked differences.

*Aplastic Anemia.* Several of the cases have come to the clinic labeled aplastic anemia. This disease is characterized by a fairly acute and fatal course, normal gastric acidity and usually a hyperchromic type of anemia with thrombopenia and the resulting hemorrhagic phenomena. No great diagnostic difficulties are therefore encountered.

*Anemia of Pregnancy.* A secondary type of anemia sometimes of a severe degree which is not uncommonly found in pregnancy, may be difficult to distinguish from idiopathic hypochromemia. However, achlorhydria is not a part of the picture and, as Osler<sup>16</sup> has pointed out, anemia of pregnancy disappears rapidly with the termination of the pregnancy or the institution of ordinary iron therapy. These facts were confirmed recently by the studies of Bland, Goldstein and First.<sup>17</sup>

*Prognosis.* As already mentioned, one of the most striking features of idiopathic hypochromemia is its persistence over long periods without much tendency to improve or become worse and in defiance of ordinary methods of therapy. Pregnancy, infections and debilitating circumstances tend to aggravate the condition, but in our experience have never led to a degree of anemia incompatible with life. The improvement which results from adequate therapy is not maintained unless this treatment is repeated at intervals. This is what is to be expected granted that the underlying defect is a deficiency of hydrochloric acid or is associated with it.

*Treatment.* The favorable response of 10 cases of idiopathic hypochromemia to fairly large doses of iron and small quantities of a copper salt was reported in the preliminary communication.<sup>1</sup> No hydrochloric acid was given to these cases. Nearly all were ambulatory patients. The treatment was suggested by the experimental observations of Hart, *et al.*,<sup>18</sup> on milk anemia in white rats and later by Whipple's group studying anemia in dogs. The preparation of iron chosen was Bland's mass. To it was added copper carbonate in the proportion of  $\frac{1}{8}$  gr. of the latter to 30 gr. of Bland's mass. These amounts were incorporated in a soluble capsule together with a small amount of a suitable laxative. The amount prescribed was 1 capsule thrice daily. Larger quantities of the copper salt

were prescribed in 5 cases, in amounts up to 5 gr. daily, but this increase resulted in a mild degree of gastroenteritis characterized by anorexia, abdominal cramps and diarrhea. The reputed toxicity of copper was discussed in the preliminary paper. For control purposes most of the original cases were placed on a preliminary

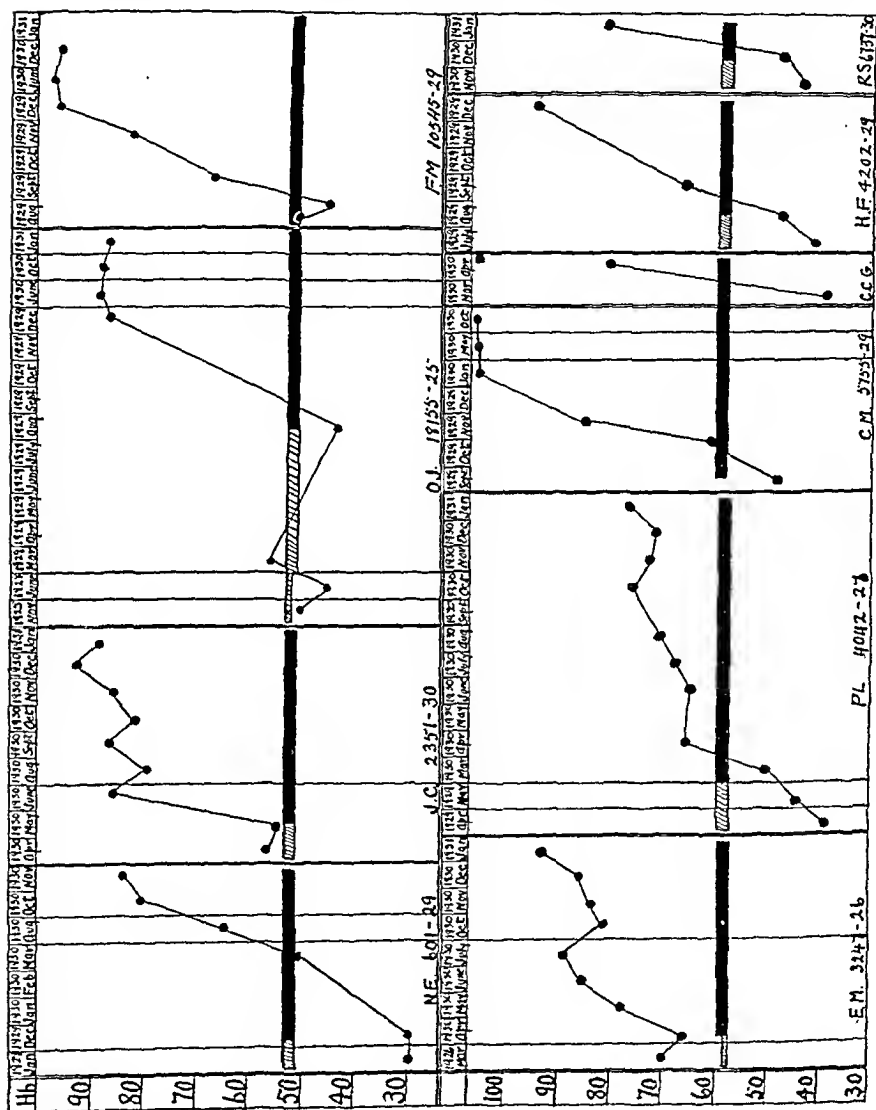


CHART 1.—Effect of treatment on hemoglobin level.

period of treatment by Bland's mass alone. Sixty grains were given daily. This treatment was persisted in for 4 weeks prior to the iron and copper trial. In 5 cases the control period was much longer than 4 weeks. No hydrochloric acid was given unless the cases proved refractory to the iron and copper mixture. The effect of the iron-copper capsules on the hemoglobin in 19 of the 22 cases

is graphically represented in the charts. Of the 3 cases uncharted, 1 could not be traced, and the other 2 are reported by their family physician to be quite well, though we have not had an opportunity to check their blood. Of the 19 cases recorded in the charts, little need be said. The results are classified as good in 16 cases, fair

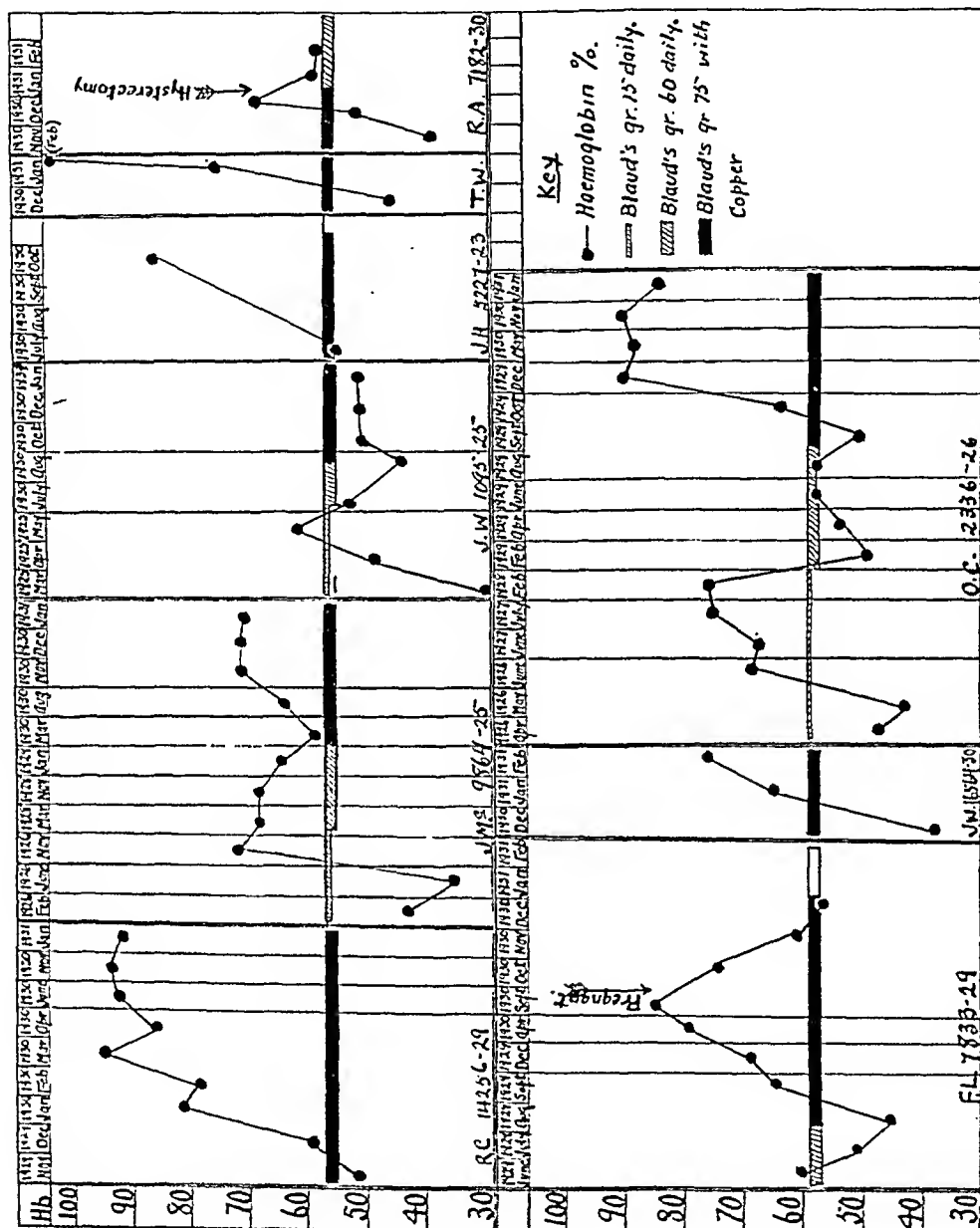


CHART 2.—Effect of treatment on hemoglobin level.

in 1 case and poor in 2 cases. In most instances there was only a slight rise or no improvement in the hemoglobin level on the Bland's mass while a decided increase in the hemoglobin promptly followed the addition of copper to the mixture. Not the least striking improvement was the patient's color. The appetite returned, and

with it a sense of well-being and a gain in weight. Two cases became pregnant after a sterile period of 5 and 7 years respectively.

The original cases have now been followed for  $1\frac{1}{2}$  years since beginning this therapy and all cases showing improvement have maintained this improvement, with the exception of the 2 cases which became pregnant, though there appears to be a tendency for the hemoglobin level to decline unless therapy is repeated at frequent intervals.

There have been 2 failures (J. W. and J. Mc.). These cases have both been anemic for many years—one has been under observation 5 years and the other 7 years. Both have been tried on liver, liver extract, Bland's mass, the iron and copper mixture, and are now being tried on iron and copper with hydrochloric acid, so far without much success. There has been no complicating factor and a recent complete check-up has not yielded additional information. The superiority of iron and copper therapy over iron alone in the treatment of this disease has been confirmed by Waugh. Giffin and Watkins<sup>30</sup> have failed to obtain results with the independent administration of copper and manganese in such cases. This failure would tend to support the contention that it is the iron which is the necessary hemoglobin building substance, but that it is rendered more available by the action of the combined copper.

The question of the relative efficiency of large doses of Bland's with and without dilute hydrochloric acid is still being debated. Mettier and Minot believe that iron acts better when given in an acid medium as with dilute hydrochloric acid. Witts, on the other hand, has emphatically stated that the giving of dilute hydrochloric acid with iron in no way enhances its therapeutic value. He has achieved success in treating this idiopathic type of anemia with large doses of iron alone, though improvement began only after the first month of therapy. If this holds true many of our control periods were too short. In 5 cases, however large doses of Bland's (60 gr.) were given for many months prior to the iron and copper therapy without any improvement in the anemia. Be this as it may, the addition of small amounts of copper would seem to render the iron more readily available as a hemoglobin builder.

In Germany<sup>31</sup> the disease has been treated successfully with ferrum reductum in 1 gm. doses. As Bland's is only 10 per cent iron this amount of reduced iron corresponds to 154 gr. of Bland's—a rather heroic dose of iron. Four cases in our series were given capsules containing 1 gm. of reduced iron in order that the results might be compared with the iron-copper therapy. The treatment was stopped when on 2 successive occasions 3 of the 4 patients reported severe abdominal cramps, vomiting and diarrhea, indicating a chemical gastroenteritis. This complication has occurred only once to our knowledge with the capsules of iron and copper, though a mild laxative action has been frequently noted.

No explanation of the mode of action of copper has been offered.

It was originally suggested by Hart, *et al.*, that the copper acted as a catalyst improving the absorption of the iron from the intestinal tract. Whether this is so or whether the copper is absorbed along with the iron and serves in the synthesis of hemoglobin is a problem not likely to be entirely elucidated until more light is brought to bear upon the nature of hemoglobin molecule. Although it is probably true that many cases of idiopathic hypochromemia are benefited by massive doses of iron in the form of Bland's mass if the treatment is persisted in a sufficient length of time, it would seem that the addition of copper renders the iron more effective, bringing about a more rapid and complete restoration of the blood values.

**Summary and Conclusions.** Evidence for considering idiopathic hypochromic anemia or hypochromemia as a disease entity is presented and 23 cases of the disease are reported.

The disease is confined to the female and runs a very chronic course with symptoms common to any moderately severe anemia.

The important clinical features are absence or great diminution of free hydrochloric acid in the gastric contents, absence of etiologic factors, a hypochromic blood picture, and a tendency to resist ordinary forms of anemia therapy.

Twenty-one of 23 cases have been treated successfully with a capsule containing Bland's mass and copper carbonate. Many of these cases had proved refractory to the iron alone before beginning the iron-copper therapy.

NOTE.—The author wishes to acknowledge his indebtedness to Charles E. Frosst & Co. for preparing and donating the capsules, and for other assistance.

NOTE.—Since this paper was submitted for publication, Adamson and Smith have reported identical results from iron-copper therapy in a series of ten cases of this disease. (Can. Med. Assn. J., 1931, 24, 793.)

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## REVIEWS.

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**HYPERTENSION AND NEPHRITIS.** By ARTHUR M. FISHBERG, M.D., Associate Physieian to Beth Israel Hospital; Adjunct Physician to Mount Sinai Hospital, New York City. Pp. 619; 38 illustrations, 1 colored plate. Philadelphia: Lea & Febiger, 1931. Price, \$6.50.

THIS book is primarily a statement for the practitioner of our present knowledge concerning hypertension and the various forms of nephritis. The earlier chapters take up the pathologic physiology of renal function; the tests of renal function; albuminuria and urinary casts; edema, uremia; arterial hypertension; hypertensive encephalopathy and hypertensive retinopathies. Then the various types of kidney disease are considered, the classification used being practically that of Volhard and Fahr. The presentation is thorough and complete, with numerous references to original sources and careful statement of controversial points. In addition to a thorough knowledge of his subject, the author brings to his task sound judgment and an ability for clear and forceful expression. Ample testimony of this is the fact that the first edition was exhausted within a year of its publication. The new edition has been thoroughly revised and includes much new material that accounts for an increase of 53 pages. The book is one that is highly to be recommended both to internists and to general practitioners.

R. K.

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**ACCIDENTAL INJURIES.** By HENRY H. KESSLER, A.B., M.D., F.A.C.S., F.A.P.H.A., Medical Director, New Jersey Rehabilitation Clinic. Pp. 718; 157 illustrations. Philadelphia, Lea & Febiger, 1931. Price, \$10.00.

THE rapid development of industrial surgery and the medical aspects of public liability have formed a new field in medical literature. In the last few years this field has been filled rapidly by the publication of books which set forth the experiences of those who deal with large numbers of accidental injuries. They represent the most authoritative analysis of the subject by which the practitioner, industrial surgeon or the compensation board may base the prognosis and treatment. Kessler, due to his wide experience in this

type of work is particularly fitted to write a valuable book on this subject. After reviewing the history and the medicolegal aspects of compensation insurance, he takes up individually injuries to various parts of the body. He discusses the relation of injury to disease, the probably period of disability resulting from the individual injuries and the method of evaluating the disability produced. An excellent discussion is given of traumatic neurosis and of methods for detection of malingering.

An extensive section is given on occupational disease, in which are set forth the laws in the various states on the subject. Lead, benzol, mercury, arsenic, radium and other forms of poisoning are discussed as well as other occupational diseases, such as anthrax, silicosis, etc.

The last chapter on rehabilitation of the physically handicapped certainly deserves commendation.

The book is well illustrated and at the end of each chapter are given extensive references on the subject which has been discussed. Court cases are often cited briefly to illustrate specific points.

Dr. Kessler's style is analytical and statistical, and the opinions which he expresses therefore bear the weight of authority. The work should find a large field among those who are in the practice of traumatic and industrial medicine and surgery. L. F.

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DISCOVERING OURSELVES. By EDWARD A. STRECKER, A.M., M.D., and KENNETH E. APPEL, PH.D., M.D. Pp. 306; 28 illustrations. New York: The Macmillan Company, 1931. Price, \$3.00.

INTROVERTS and extroverts, the subconscious, transference, rationalization, inferiority and many other complexes (by the way, why cannot we hear more of superiority complexes?) are today such frequently used terms on the street and stage that one may feel sure that the public is on its way to becoming "mental-hygienically conscious," to continue the eacophonie jargon. Nevertheless the superficiality of such knowledge is in danger of making it the proverbial dangerous thing. "Know thyself" may well be considered the essence of wisdom, yet the "Teach thyself," that is hoped for in reading such a book in a complex field like this should certainly be supplemented by personal contact with expert instructors if the patient is to receive maximum benefit. With this qualification, simple yet sound and thoughtful books such as Riggs' "Intellectual Living," Osler's "A Way of Life," James' "The Will to Believe," and the present one written by authorities on their subject, are all the more needed to help in the preservation or restoration of normal mental mechanics. E. K.



THE HISTORY OF PÆDIATRICS. By GEORGE FREDERIC STILL, M.A., M.D. (CANTAB.), HON. LL.D. (EDIN.), F.R.C.P. (LOND.), Professor of Diseases of Children, King's College, London. Pp. 526; 12 illustrations. New York: Oxford University Press, 1931. Price, \$8.00.

MANY, even of middle age, who learned of Still's Disease in their student days, may be surprised that its first describer is still with us as Professor of Diseases of Children at King's College, London, and active. The present work in fact had to be created in "rapt hours snatched from the heavy demands of busy practice, a *πάρεργον* indeed."

Beginning with Hippocrates, the author pleasantly portrays the progress of the study of diseases of children through the ensuing 2300 years from a combined chronologic and biographic point of view. Like the history of general medicine, it portrays the activities of the classical period, the stagnation of the Dark Ages, the revival of the Renaissance, and the chief milestones of progress from then to the end of the eighteenth century. One cannot but regret that the author did not chose to pursue his topic into the important contributions of the nineteenth century. A companion to, rather than a rival of, Ruhrah's "Pediatrics of the Past," Still's History finds room for over 50 names not included in the Anthology, while of those included by Ruhrah, only Aretcus, Wurtz and Plater are omitted from Still's Table of Contents. A list is given of 213 Inaugural dissertations scattered over three centuries; but how easy would it be to double such a list: from the Elzevir press alone one could cull many a "De rachitide," "De Cholera Morbus," "De Tussa Convulsiva," "De Hydrocephalo," etc., most of which would show more mimicry than merit. In spite of a slight tendency toward biographic lexicography the book affords many a pleasant hour's reading and we are glad that the author "was too much in love with my subject to jilt it" when he came in contact with previous explorations in the same field.

E. K.

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ZEHN JAHRE FORSCHUNG AUF DEM PHYSIKALISCH-MEDIZINISCHEN GRENZGEBIET. By O.S. PROF. DR. FRIEDRICH DESSAUER, Direktor des Institutes. Pp. 403; 190 illustrations. Leipzig: Georg Thieme, 1931. Price, M. 36.

THIS work is a report of the results obtained in an institute designed for the study of the application of physics to medicine. Interest in the book is therefore narrowed to two groups, physicists, interested in apparatus and methods, and clinicians interested in certain special problems.

Of greatest interest to general medicine is the subject to which

most attention is paid in the volume—the study of the effect of air carrying a positive or negative electric charge. The problem of producing and controlling exact conditions for the experiment is discussed at length with descriptions of apparatus and methods. Increased blood pressure is lowered by inhalations of negatively ionized air; the best results in cases of climatic and essential hypertension. Positive charged air acted unfavorably and increased the blood pressure. Subacute and chronic “rheumatic” complaints reacted with increased pain and at times, objectively, with joint swelling; in a certain number of cases it is believed that a favorable therapeutic result was attained.

Most interesting is a suggestion of Dessauer, that an unknown agent in the air is perhaps the active factor, the ionization acting as an activator.

The remainder of the book is devoted to diverse problems of which the most important is a basic discussion of the biologic action of radiant energy.

J. S.

THE PHYSICIAN OF THE DANCE OF DEATH. By ALDRED SCOTT WARTHIN, PH.D., M.D., LL.D., Professor of Pathology and Director of the Pathological Laboratories in the University of Michigan, Ann Arbor. Pp. 142; 92 illustrations. New York: Paul B. Hoeber, Inc., 1931. Price, \$7.50.

Few of the thousands of tourists who annually cross the Mühlenbrücke at Luzerne can have failed to have been interested in the quaint triangular representations of Meglinger's Totentanz and few cultured people have not at least some appreciation of Holbein's “Imagines Mortis.” Never, however, has the underlying idea and its various manifestations been more accurately and entertainingly told than in the present book, reprinted from articles in the *Annals of Medical History*. The Danse Macabre, or Totentanz, has held the imagination of Europeans for over 500 years, from the earliest known example of 1424 in the Cimetière des Innocents in Paris to the numerous recrudescences brought out by the World War. Taking form at a time when plague and pestilence and a very vivid hell were everpresent horrors, it has been variously explained as the popular expression of the early Christian *memento mori*, the superstition of the midnight dance of the churchyard dead, or, as the author prefers, the neurotic response of an emotionally unstable age by taking actual pleasure in its very fear of death. The later introduced element of satire on social equality and even political and religious satires also played their parts in the sixteenth century. The author's emphasis on the physician of the series reveals not only the physician's changing costumes over 500 years but also something of his social standing and of lay concepts of the status and progress of

medicine during a long period. With the changed modern philosophy toward death, such as the author's view of its being a normal termination of an involution period—"the Totentanz mythus awaits a new birth."

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E. K.

**THE DIAGNOSIS AND TREATMENT OF BRAIN TUMORS.** By ERNEST SACHS, A.B., M.D., Professor of Clinical Neurological Surgery, Washington University School of Medicine, St. Louis. Pp. 396; 224 illustrations, 10 in colors. St. Louis: C. V. Mosby Company, 1931. Price, \$10.00.

SACHS has written a very useful book on the diagnosis of brain tumors. There has not been such a work available to medical students and those not familiar with the field. This work attempts to supply the need.

The work is logically carried out. There is an elementary chapter on the anatomy of the nervous system, giving the essential details necessary for diagnostic purposes. There is a good chapter on methods of examining the nervous system, and a useful chapter on the surgical pathology of brain tumors. Following these elementary chapters there follows a discussion of the signs and symptoms of tumors in the various regions of the brain. The chapter on the differential diagnosis of brain tumors and conditions which may simulate them is interesting, and the final chapter on operative technique will prove useful in giving an understanding of neurosurgical methods to those who are unfamiliar with them.

The book suffers from being too elementary. For this reason it will prove much more useful to medical students than to specialists in the field of neurology or neurologic surgery.

B. A.

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**PRIMARY SYPHILIS IN THE FEMALE.** By THOMAS ANWYL DAVIES, M.D. (LOND.), Director of the Whitechapel (L. C. C.) Clinic. Pp. 120; 25 illustrations, 17 in colors. New York: Oxford University Press, 1931. Price, \$4.00.

THIS monograph is a work of distinction in its field, both in matter and format. The author draws on probably the largest and most thoroughly studied material of its kind in existence, to correct many misimpressions in regard to the onset of syphilis in the woman, a problem full of significance for both individual and public health. From a massive series of 584 personally examined cases in the key clinic of the British venereal disease service, St. Thomas' Hospital, the author shows that the chancre in the woman is internal in 45 per cent of cases, and usually on the cervix, a point raising most important questions as to the mechanism of infections and the nature of the infecting agent in the male. The symptoms

of primary syphilis in the woman, the types of lesions, the differential considerations, the confusion with carcinoma and gumma, non-venereal vaginal conditions, such as trichomonas infections, are all dealt with in systematic and terse fashion, and with gratifying completeness. The photography especially, to one who knows the regional difficulties, is remarkable, and, while the Reviewer holds in general no brief for colored plates, these are very much above the average and really instructive. The review of the literature carried through the text discussion is clear, discriminating and extensive. It is interesting to see how large an error based on impression of an occasional case may loom. The book can be commended to practitioners and, of course, most emphatically to gynecologists, venereologists and officers of public health clinics who need it as a desk reference.

J. S.

## BOOKS RECEIVED.

### NEW BOOKS.

*Cosmic Consciousness.* By RICHARD MAURICE BUCKE, M.D., Formerly Medical Superintendent of the Asylum for the Insane, London, Canada. Pp. 384; 1 illustration. New York: E. P. Dutton & Co., Inc., 1931. Price, \$5.00.

*Bedside Interpretation of Laboratory Findings.* By MICHAEL G. WOHL, M.D., Associate Professor of Experimental Medicine, Temple University Medical School, Philadelphia. With an Introduction by JOSEPH McFARLAND, M.D., Sc.D., Professor of Pathology, University of Pennsylvania. Pp. 321; 133 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, \$6.00.

*Encephalitis Lethargica, Its Sequelæ and Treatment.* By CONSTANTIN VON ECONOMO, Professor of Psychiatry and Neurology in the University of Vienna. Translated and adapted by K. O. NEWMAN, M.D., Pathologist to the Oxford County and City Mental Hospital, Oxford. Pp. 200; 21 illustrations. New York: Oxford University Press, 1931. Price, \$6.00.

*Cutaneous X-ray and Radium Therapy.* By HENRY H. HAZEN, A.M., M.D., Professor of Dermatology, Medical Department of Georgetown University. Pp. 166; 28 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, \$3.00.

*The Causation of Chronic Gastro-duodenal Ulcers. A New Theory.* By J.-JACQUES SPIRA, M.R.C.S. (ENG.), L.R.C.P. (LOND.), with an Introduction by SIR HUMPHREY ROLLESTON, BART., G.C.V.O., K.C.B., Physician in Ordinary to H. M. the King. Pp. 78. New York: Oxford University Press, 1931. Price, \$2.50.

*Asthma and Hay Fever in Theory and Practice.* In three parts. *Part I. Hypersensitiveness, Anaphylaxis, Allergy.* By ARTHUR F. COCA, M.D., Professor of Immunology, Cornell University Medical College. *Part II. Asthma.* By MATTHEW WALZER, M.D., Instructor in Applied Immunology, Cornell University Medical College. *Part III. Hay Fever.* By AUGUST A. THOMMEN, M.D., Lecturer in Medicine, University and Bellevue Hospital Medical College. Pp. 851; 95 illustrations and 7 charts. Springfield, Ill.: Charles C Thomas, 1931. Price, \$8.50.

- Modern Proctology.* By MARION C. PURITT, M.D., L.R.C.P., S. (EDIN.), F.R.C.S. (EDIN.), F.A.C.S., Associate in Surgery, Emory University School of Medicine, Atlanta. Pp. 404; 233 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, \$8.00.
- Fractures of the Jaws.* By ROBERT H. IVY, M.D., D.D.S., F.A.C.S., Professor of Maxillo-facial Surgery, Graduate School of Medicine, and of Clinical Maxillo-facial Surgery, School of Dentistry, University of Pennsylvania, and LAWRENCE CURTIS, A.B., M.D., D.D.S., Assistant Professor of Maxillo-facial Surgery, Graduate School of Medicine and School of Dentistry, University of Pennsylvania. Pp. 180; 177 illustrations. Philadelphia: Lea & Febiger, 1931. Price, \$4.50.
- United Fruit Company Medical Department 19th Annual Report, 1930.* Pp. 276; 31 illustrations.
- The Great Physician. A Life of Sir William Osler.* By EDITH GITTINGS REID. Pp. 299; 10 illustrations. New York: Oxford University Press, 1931. Price, \$3.50.
- Medicine, Science and Art.* By ALFRED E. COHN. Pp. 212. Chicago: The University of Chicago Press, 1931. Price, \$4.00.
- Injuries and Sport.* By C. B. HEALD, C.B.E., M.A., M.D. (CANTAB.), M.R.C.P. (LOND.), Physician, with Charge of Electro-therapeutic Department, Royal Free Hospital. Pp. 543; 380 illustrations. New York: Oxford University Press, 1931. Price, \$8.00.
- The Medical Clinics of North America, Vol. 15, No. 1 (Mayo Clinic Number—July, 1931).* Pp. 263; 56 illustrations. Philadelphia: W. B. Saunders Company, 1931.
- Diagnosis in Joint Disease.* By NATHANIEL ALLISON, M.D., F.A.C.S., Professor of Surgery, in charge of Division of Orthopedic Surgery, University of Chicago, and RALPH K. GHORMLEY, M.D., Associate in Orthopedic Surgery, The Mayo Clinic. Pp. 196; 215 illustrations—11 in color. New York: William Wood & Co., 1931. Price, \$9.00.
- Medical Jurisprudence.* By CARL SCHEFFEL, PH.B., M.D., LL.B. Pp. 313. Philadelphia: P. Blakiston's Son & Co., Inc., 1931. Price, \$2.50.
- Breast-Feeding.* By MARGARET EMSLIE, M.D., CH.B., Late Senior Assistant Medical Officer for Maternity and Child Welfare, County Borough of Croydon. Pp. 142; 6 illustrations. New York: Oxford University Press, 1931. Price, \$2.00.

## NEW EDITIONS.

- Manual of Surgery, Vol. 1. General Surgery.* By ALEXANDER MILES, M.D., LL.D., F.R.C.S. (EDIN.), Consulting Surgeon, Royal Infirmary, Edinburgh, and D. P. D. WILKIE, M.D., F.R.C.S. (EDIN. and ENG.), Professor of Surgery, University of Edinburgh. Pp. 574; 176 illustrations. Eighth edition. New York: Oxford University Press, 1931. Price, \$3.80.
- Diseases of the Gums and Oral Mucous Membrane.* By SIR KENNETH GOADBY, K.B.E., M.R.C.S., L.R.C.P., D.P.H. (CANTAB), Lecturer on Bacteriology of the Mouth, Dental Department, University College Hospital. Pp. 496; 146 illustrations. Fourth edition. New York: Oxford University Press, 1931. Price, \$13.00.
- Practical Zoölogy. Revised Edition.* By ROBERT W. HEGNER, PH.D., Professor of Protozoölogy, Johns Hopkins School of Hygiene and Public Health. Pp. 561; 332 illustrations. New York: The Macmillan Company, 1931. Price, \$1.80.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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**The Coronary Artery in Health and Disease.**—HERRICK (*Am. Heart J.*, 1931, 6, 589), in the latter part of his Harvey Lecture, discusses the theories that have been advanced to explain the mechanism of production of heart pain. He writes that there are two prevalent theories to explain the causation of this pain: The one, the aortic theory, holds that pain is due to stretching of the diseased wall of the great vessel. Allbutt was the first serious protagonist of this idea, and after him Wenckebach, Schmidt and Vaquez. The older theory, the one that has been prevalent since the time of Parry and Jenner, maintains that the explanation of the symptom complex lies in perversion of the function of the coronary artery or the muscle supplied by that artery, or by both. In substantiation of this thesis, the author advances arguments which have been proposed in the past, and in addition he suggests that a few of the more recent and more exact physiologic and chemical studies may add additional corroboration to the coronary theory. The arguments that appeal to him especially, and they are more or less old arguments, are, that the negative finding of coronary disease in a certain number of cases may be explained on the basis of incomplete examination of these vessels or, if this is not the explanation, that the disease itself is due to a disturbance of function and the anatomic lesion is not the disease; that angina is very infrequently found with auricular fibrillation, it is rare with "chronic myocarditis" and it is extremely unusual to have anginal attacks when the patient is suffering from far-advanced syphilitic aortitis unless the coronary months are involved by this process; that the nitrites and theobromin compounds are dilators of coronary vessels and relieve pain; that epinephrin occasionally provokes anginal attacks in patients given this drug if they are subject to such attacks,

whereas in the young individual with coronary arteries which presumably are not abnormal these injections do not produce pain. A somewhat more modern concept and argument in favor of coronary disturbance is that hypoglycemia, produced by insulin, occasionally produces anginal distress in those subject to angina, as a result of the still further reduction of nutrition to the heart muscles as a result of arterial narrowing; in severe anemia a diminished amount of oxygen to the heart muscle under stress may produce pain; in hyperthyroidism anginal pain may occur in those with damaged coronary arteries because the heart muscle cannot receive a sufficient quantity of blood to meet the requirements of increased metabolism. The electrocardiographic evidence obtained during periods of attacks exhibits variations in ventricular complexes which disappear following the attack and would seem to indicate transitory changes in the heart muscle. In a certain number of instances of Raynaud's disease the vasomotor phenomena have been correlated with angina, and, lastly, of the arguments to substantiate his ideas, the author is rather inclined to the opinion that animal experimentation would indicate that temporary occlusion of the coronary brings on pain. The author is not dogmatic nor is he assertory. He gives the impression that it is largely a matter of opinion as to which view is accepted concerning the cause of anginal pain, but he states definitely that it is only through coöperation of the internist and pathologist, the experimental physiologist and the electrocardiographer that it would be possible to pile up evidence which would show conclusively just how anginal pain is produced.

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## SURGERY

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UNDER THE CHARGE OF  
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PHILADELPHIA, PA.

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**Gastric Syphilis.**—O'LEARY (*Am. J. Surg.*, 1931, 11, 286) report that 89 of a group of 151 patients with gastric lesions and syphilis were found to have gastric syphilis. These were selected from among approximately 25,000 patients with syphilis. The diagnosis was based on the combined results of prolonged therapeutic tests, histopathologic studies, morphologic changes in the roentgenologic characteristics and restoration of gastric function. The demonstration of the existence of other evidence of clinical syphilis is not pertinent to the diagnosis of gastric syphilis. Of the 89 patients with gastric syphilis 73 per cent had positive Wassermann reaction of the blood as the only other evidence of syphilis and 6 per cent had negative serologic reactions. The incidence of clinical signs of syphilis was almost as high in these cases with gastric carcinoma (16 per cent) as it was in those with syphilis of the stomach (27 per cent). Recognition of the *Spirochaeta pallida* in excised gastric tissue as the conclusive means of diagnosis is a diagnostic requirement demanded by the scientific purist. The author would prefer to see among the diagnostic criteria for gastric syphilis one demanding a histopathologic study to eliminate carcinoma. Although

the *Spirochæta pallida* may be demonstrated in the gummatous type of gastric ulcer, in cases of diffuse syphilitic fibrosis the organism has not as yet been recognized. Numerous instances of the bizarre character of both the clinical and microscopic features of gastric syphilis merely confirm the knowledge that syphilis is a protean disease. The result of treatment in the fibrosed syphilitic stomach is unsatisfactory and plastic gastric operation offers slight help. As in all forms of syphilis, early diagnosis and early institution of treatment are rewarded by a higher incidence of cure than is obtained otherwise, a fact forcibly emphasized by this study.

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**Spondylitis Deformans.**—KLEINBERG (*Arch. Surg.*, 1931, 22, 485) writes that spondylitis deformans is a chronic disease of the back, characterized by increasing stiffness and deformity of the spine, back-aches, pains in the head, chest or extremities and impairment of health. Although there are numerous causes of this disease, the final pathologic change is the same in all varieties. The most disabling feature of this disease is the flexion deformity of the spine. Treatment, to be effective, must be instituted before there is complete bony ankylosis of the spine. The deformity can be corrected, or at least reduced by continuous treatment on a convex frame, supplemented by physiotherapy, stretching of the back and voluntary corrective exercises. Following the correction of the deformity a favorable result can be assured only by a long period of support of the back in a spinal brace.

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**Attitudes Associated With Lesions About the Hip Joint.**—HART (*Arch. Surg.*, 1931, 22, 463) states that the attitudes of the following lesions about the hip are discussed, namely, infantile scurvy, rickets and syphilitic epiphysitis associated with pseudoparalyses; tuberculosis of the hip, spontaneous or pathologic dislocation of the hip; septic arthritis of the hip; chronic deforming arthritides, epiphyseal coxa vara or separation of the upper femoral epiphysis; traumatic dislocations of the hip; malum coxæ senilis or hypertrophic arthritis of the hip and fracture of the neck of the femur. Certain lesions about the hip joint present fairly constant attitudes of the lower extremities and have definite relations to age periods. There are a number of factors that determine the attitude of the lower extremities; the factors that determine the malposition in an individual case cannot always be satisfactorily explained. A correct interpretation of the attitude of the lower extremities cannot be made unless the pelvis is placed in the normal anatomic position with reference to the transverse and horizontal plane and the lumbar spine is flat. The frog attitude in a child should lead the physician to suspect one of the pseudoparalyses associated with rickets, scurvy or syphilitic epiphysitis. The position of instability of the hip joint, flexion, adduction, internal rotation, is productive of spontaneous dislocation and should be considered a dangerous attitude. Epiphyseal coxa vara is a hazard of adolescent life and fracture of the neck of the femur is a hazard of old age. The attitude of the involved extremity in each condition is similar, *i. e.*, abduction and external rotation. Infection of the hip joint presents a constant malposition of flexion combined with either abduction and external rotation or adduction and internal rotation.



**Prostatic Abscess.**—SARGENT and IRWIN (*Am. J. Surg.*, 1931, 11, 334) say that in any acute prostatic inflammation there is complete safety in waiting until careful observation has permitted a definite diagnosis of frank abscess formation. Both prostatic lobes should be opened whether or not the signs indicate bilateral abscess formation. Any method involving opening of the abscess into the posterior urethra entails unnecessary risk of persisting urethritis from false cavity formation. Drainage through external urethrotomy unduly lengthens morbidity, favors the development of complicating epidymitis and entails the unnecessary risk of a more or less persistent urinary fistula. No method offers greater freedom from complications and sequelæ or more certain cure of the disease than that of radial perineal dissection with posterior prostatotomy.

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**Periosteum.**—LEADBETTER (*Arch. Surg.*, 1931, 22, 754) declares that autogenous periosteum has a definite tensile strength which does not vary when it is brought into contact with free body fluids. It is easily obtained from the broad anterior surface of the tibia. If care is taken in the removal of the periosteum to elevate the small particles of the outer layer of the cortex, it is definitely osteogenic when placed in contact with cortical bone. Periosteum proliferates best when the grafted bone is thoroughly immobilized. Its proliferation in immobilized bone is rapid and early. It does not interfere with the circulation in the fragmented ends, but rather increases the circulation of this region, thereby offering an aid to the formation of late callus. The use of the periosteal suture allows mobilization of the fractured extremity at an early date.

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**Mixed Tumors of the Parotid Gland.**—MERRITT (*Am. J. Surg.*, 1931, 25, 507) claims that the treatment of mixed tumors of the parotid gland is largely in the hands of the radiologist, high voltage roentgen therapy being a useful adjunct to radium in these cases and is generally indicated. While a small encapsulated tumor may be successfully excised, it appears from the accumulated evidence that implanted radium will accomplish equally as good results. A combination of surgical removal and irradiation by either radium or Roentgen ray is illogical. If the former is adequate, the latter is superfluous. A failure to destroy the tumor by implanted radium or radon at the initial attempt, does not induce the serious complication of increased malignancy which frequently follows in adequate surgical removal. Additional radium treatments may be given until maximum result is obtained.

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**Perinephritic Abscess.**—BIRDSALL (*J. Urol.*, 1931, 25, 405) says that 11 cases of perinephritic abscess in this series followed infection, extrarenal in origin. In 4 cases where the abscess was renal in origin, 2 were secondary to renal tuberculosis, 1 to renal lithiasis and 1 to tumors of the kidney. In 1 case there was no etiology ascertainable. Perinephritic abscess of extrarenal origin, in most cases, is the result of hematogenous metastasis of the infecting organisms to the renal cortex followed by cortical abscess with direct extension to the perirenal tissue. Perinephritic abscess may also result from lymphatic metastasis of the infection. The most common organism found is the *Staphylococcus aureus*. There were no hospital deaths.

## THERAPEUTICS

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**The Treatment of Obesity With Thyroxin.**—Because of the widely varying amounts of thyroid preparation advocated for the treatment of obesity, HELLFORS (*München. Med. Wchnschr.*, 1931, No. 20, 826) undertook a reinvestigation of the problem. The cases studied exhibited pronounced obesity. Constant weight on a standard diet was maintained during a control period after which initial doses of 0.5 mg. of thyroxin were administered three or four times daily by mouth. The frequency of administration was raised to five or six times daily depending on the clinical effect of the drug. Without exception, the subjects began to lose weight slowly within 2 or 3 days after the initial administration. With a daily dose of 2 mg. of thyroxin there was an average loss of 0.2 to 0.3 kg. daily. No diuresis was noted. The general condition of the patients remained good although the basal metabolism usually rose 30 to 40 per cent. The total amount of thyroxin used for the individual patient varied from 18 to 60 mg. The total loss of weight varied from 3 to 7 kg. within 17 days. Temporary manifestations of hyperthyroidism were observed only in cases where the dosage was high. A comparison of various preparations of thyroxin from different pharmaceutical houses showed considerable divergence. Thus 0.5 mg. daily of thyroxin "Henning" produced an average rise of 2 per cent in the basal metabolism; 2 mg. daily of thyroxin "Schering," on the other hand, raised the metabolism only 1 per cent; while 1 mg. daily of thyroxin "Hoffmann-LaRoche" caused a rise of 1 per cent. The carbohydrate metabolism, as judged by sugar-tolerance curves, remained uninfluenced by thyroxin. There was a rise of as much as 30 per cent in the lymphocyte counts at the height of the treatment. No changes were apparent in the circulatory system. The earliest manifestation of overdosage was mental irritability. Perspiration, tremor and changes in menstruation appeared later.

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**Muscle Extract in the Treatment of Angina and Intermittent Claudication.**—KORACH (*München. med. Wchnschr.*, 1931, No. 12, 473) reports on the therapeutic effect of a muscle extract called "Myol" in 70 cases of angina pectoris. Sixty cases of this group suffered from true angina and 10 from pseudoangina. They had received no other treatment. Because the beneficial effect of oral administration is slow and gradual, this channel of administration was not used. Fifteen or 20 minutes after subcutaneous and even more promptly after intramuscular and intravenous administration of the extract, there was a

distinct improvement in the patient's condition. The pain became less intense and the patients were able to move about comfortably. The objective changes were a decrease in the degree of tachycardia and a lowering in the blood pressure of from 10 to 30 mm. of mercury. The capacity to walk increased in cases suffering from anginal pain on moderate exertion. The duration of the effect of a single injection was 24 hours. Following this period the complaints returned but with less intensity. In addition, the muscle extract was also found beneficial in cases with intermittent claudication. In a number of instances the daily administration of the extract was changed after 3 weeks to injections every alternate day. Later the clinical improvement was sufficiently great to make oral administration satisfactory. The author claims that the beneficial effect of the extract is not due to a nonspecific protein reaction, since the cases that responded beneficially to the extract did not respond to protein therapy.

**Digitalis Dosage.**—WEESE (*Deutsch. Med. Wchnschr.*, 1931, 57, 625) presents the results of a series of studies employing a standardized form of Starling's heart-lung preparation into which various surviving organs may be introduced at will for perfusion. He was able to establish the fact that the perfused heart of the cat removed quantitatively from the perfusion fluid a fixed amount either of digitoxin or strophanthin in relation to its own weight. This amount was constant for different hearts and was the minimal lethal dose. The amount removed was characteristic for each glucoside and bore a fixed relation to the minimal fatal dose for the cat when administered intravenously. For digitoxin the heart removed by  $\frac{1}{16}$  of the minimal lethal intravenous dose as its own minimal lethal dose by perfusion; for strophanthin the ratio was  $\frac{1}{11}$ . The author confirms the well known fact that the digitalis glucosides disappear almost immediately from the blood stream and he concludes that the remaining  $\frac{15}{16}$  of the fatal dose of digitoxin or  $\frac{10}{11}$  that of strophanthin are removed by immediate fixation in other organs of the body following intravenous injection. By the perfusion of various organs including voluntary muscle and the injection of doses of the glucosides into the circulation leading to these organs so that they must first pass through the perfused organ before reaching the heart, he establishes the fact that all tissues of the body except the lungs participate in this immediate adsorption of the glucosides, the most important being voluntary muscle and the liver. He also shows that the rate of absorption by the heart is influenced by the concentration of the glucosides, although this does not alter the total amount absorbed. Furthermore, the proportional utilization of the glucosides by the heart as compared to the remaining tissues of the body increases as the concentration of the drug in the blood stream diminishes. Thus the maximal effect upon the heart is best secured by slow intravenous injection. Dilatation and hypertrophy of the heart increase its capacity to absorb the glucosides, probably by increasing its surface area and that of its vascular system. Contrary to this, exhaustion of the heart, especially by reducing the soluble phosphatids and calcium salts, diminishes its capacity to bind the glucosides. Inasmuch as these latter conditions are believed to prevail in the presence of cardiac disease, it is suggested that they tend to offset the great susceptibility of the heart which results from its dilatation and hypertrophy.

## PEDIATRICS

UNDER THE CHARGE OF

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**Evaluation of the Results of Tonsillectomy and Adenoidotomy.**—SELKIRK and MITCHELL (*Am. J. Dis. Child.*, 1931, 42, 9) point out that there are 11 methods of approach to a study of the effects of tonsillectomy and adenoidotomy. Their study was an attempt to use the method commonly employed by other investigators, but with a smaller group of children, so that more intensive study of them could be made than is possible in dealing with a larger group. At first they planned to compare the changes in their group of 130 tonsillectomized children with those of a similar group of controls, but this plan was abandoned because the group was rather small, but still more because it was deemed faulty for other reasons. Nevertheless, because of the thoroughness of the investigation it was decided to present the report. They found that 3 years after tonsillectomy there was a lessened incidence of colds, nasal obstruction and sore throat, while sinus infection, headache and growing pains were increased in frequency. As a criticism of their own study and that of many others, they note certain modifying factors to which no attention or too little attention is paid. These are age, sex, race, heredity, financial class, season, the effect of adenoidotomy alone, length of observation after operation, source from which the history was obtained, incidence of tonsillectomy in the community at large, and the suitability of the control group. The neglect of these factors often invalidates the conclusions. There are several methods of approach in evaluating the results. The method of choice varies with the symptoms studied. The method of studying a large number of symptoms and pathologic conditions simultaneously usually results in superficiality. Separate and intensive studies of a single symptom in relation to tonsillectomy have been made mainly on the rheumatic syndrome and probably offer the best means of approach of studying the other symptoms. Many of the symptoms and conditions popularly supposed to be associated etiologically with diseased tonsils are those in which the natural course and incidence, regardless of the effect of tonsillectomy, are not known. Many of them, also, are affected by other factors than tonsillectomy in an as yet unknown manner. It would seem that the conclusions drawn from some of the studies which are widely quoted as showing the effects of tonsillectomy are decidedly open to question because of the failure to consider other factors in evaluating the results.

**Mineral Metabolism in Late Rickets.**—STEARNS, OELKE and BOYD (*Am. J. Dis. Child.*, 1931, 42, 88) followed the progress of two girls by means of roentgenograms and chemical studies over a period of several months. They noted definite roentgenologic evidence of calcification

of bone. Both children during the period of healing rickets, retained ample quantities of calcium and phosphorus. The manner of excretion of these elements was similar in both children to that observed in infantile rickets with the exception that the urinary excretion of calcium remained low during the period of healing, instead of increasing, as has been noted usually in healing of infantile rickets. The acid-base relationships of the urine and the retention of total fixed base of these children were not conspicuously different from those of a child of the same age, who had no abnormalities of the bone. The serum calcium in each child was at all times within normal bounds. The serum inorganic phosphorus of each child remained consistently low, between 2 and 3 mg. per hundred cc., during the entire period of study, although the rachitic condition was markedly improved in both children.

**The Treatment of Chorea by Induction of Fever.**—SUTTON (*J. Am. Med. Assn.*, 1931, 97, 299) says that the evaluation of any method of treating a disease like chorea, which has several grades of severity, and which, when untreated, has such a variable duration, is very difficult. Many patients apply at a hospital after weeks or months of illness. Others come within a week or two of the onset, and occasionally a case develops in the ward. It is well known that the average attack improves with rest and quiet and is over in from 6 to 10 weeks, even without any other treatment. It is equally well known that the slightest twitchings of a mild attack may persist for months. Sometimes an attack will continue in all of its severity for a long period. Formerly the author was accustomed to isolate the patients as well as possible. They were kept quiet in bed until all choreiform movements were gone. Various drugs and other methods of treatment, such as arsenic, calcium bromide, salicylates, thyroxin and cold packs were tried at different times without noticeable effect on the course of the disease. The present method of treatment has changed the outcome so that it is possible to expect the average patient to be ready for discharge in about 3 weeks after admission, unless the discharge is delayed by some other illness, by operation such as tonsillectomy, or by waiting for a vacancy in a convalescent home. This new method has been used for too short a time to warrant any comment on the possible effect on recurrences or the development of heart disease. The author treated 24 cases of chorea with intravenous injections of typhoid-paratyphoid vaccine as a means of producing fever. The results thus far were good. There was prompt cessation of the symptoms, and the course of the disease seemed to be greatly shortened. In the cases reported the average duration of treatment was from 8 to 9 days. A drug that has been used in the treatment of chorea is phenyl-ethyl-hydantoin. Its benefit is also derived from the production of a febrile phase. The advantages of the typhoid-paratyphoid vaccine over this drug are that the febrile reaction can be produced immediately without the necessity of waiting for a period up to 2 weeks for intoxication to develop. All cases respond to the typhoid-paratyphoid reaction while not all cases develop the intoxication and fever with the phenyl-ethyl-hydantoin, even when given over long periods. The typhoid-paratyphoid vaccine has not caused any complications such as severe skin eruptions, agranulocytosis, bronchopneumonia and nephritis, which have been described

with phenyl-ethyl-hydantoin. By increasing the dose of the vaccine, or when giving it again several weeks after a course of injections, fever can always be produced.

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**The Antirachitic Potency of the Milk of Cows Fed Irradiated Yeast or Ergosterol.**—HESS, LEWIS, McLEOD and THOMAS (*J. Am. Med. Assn.*, 1931, 97, 370) found that cow's milk was made highly antirachitic by means of supplementing the fodder with irradiated ergosterol or with irradiated yeast. These milks of various potencies were given to a large series of infants during the winter. By this means rickets was prevented except in its minor manifestations, and roentgenologic rickets did not develop. In cases in which rickets was already present, the milk brought about calcification within a month. From the point of view of the number of antirachitic rat units fed to the cow, the irradiated yeast induced a more potent milk than the viosterol. This distinction was evident both by biologic assay on rats and by clinical tests of a preventive and curative nature. The outstanding advantage of this method of antirachitic therapy is that it functions automatically as the specific factor is incorporated in the diet of the infant.

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**Soft-curd Milk: Nature's Food for Infants.**—HILL (*Arch. Ped.*, 1931, 48, 417) states that when soft-curd milk is available, the feeding problem becomes much simpler. Experimental results would indicate that this milk is easily digested without dilution or modification, and that it can be used in a concentrated form. Since there is no dilution, the normal sugar content of the milk is sufficiently high not to require the usual addition of carbohydrate. The use of lactic acid to produce an acid curd apparently is not necessary when soft-curd milk is used. It seems possible to supply milk that is sweet and has a normal reaction and has not been abnormally sweetened, nor any other alterations made from its natural state. The use of a natural milk obviously is superior to the use of a milk that is abnormally acid or alkaline in its reaction. There has been an advantage noted in the use of hard-curd milk over soft-curd milk in the manufacture of cheese. This may ultimately free soft-curd milk for use in infant feeding.

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## DERMATOLOGY AND SYPHILIS

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**Untoward Results From the Use of Gold Compounds.**—DRIVER and WELLER (*Arch. Dermat. and Syph.*, 1931, 23, 87), in reporting a fatality following the administration of 25 mg. and 50 mg. of gold and

sodium thiosulphate 4 days apart in a woman with lupus erythematosus, take occasion to review the gold compounds in common use and the reactions following their administration, and cite from the literature numerous examples of deaths arising in the course of gold therapy in cutaneous as well as pulmonary tuberculosis. The paper is particularly timely in view of the more widespread knowledge of the value of the salts of gold in lupus erythematosus and their more indiscriminate trial in the tuberculids and closely related dermatoses. The more important reactions from the use of gold may be tabulated as follows:

*A. Immediate Reactions.* (1) Anaphylactic type—varying degrees of syncope and shock, with nausea, occasional vomiting, flushed face, edema of the lips and face and tachycardia. These symptoms are usually of short duration, but death has resulted. (2) Mild febrile reaction with malaise and headache, usually lasting 4 to 6 hours and rarely for several weeks. (3) Metallic taste in the mouth. (4) A foreign protein reaction, which usually begins about 1 hour after injection, characterized by dull headache, suffusion of the eyes and chill. The symptoms abate within about 0.5 hour.

*B. Delayed Toxic Reactions.* (1) A syndrome of fever, headache, nausea, occasionally with vomiting, malaise and prostration. Symptoms begin 4 to 6 hours after injection and last from a few days to a week or longer. (2) Stomatitis and gingivitis, usually mild but rarely of an ulcerative and hemorrhagic type. (3) Renal damage—albuminuria and varying degrees of acute nephritis. (4) Hepatitis with icterus. (5) Digestive disturbances ranging from the transient symptoms of the toxic syndrome to ulcerative and hemorrhagic enteritis. (6) Cutaneous eruptions: The picture varies greatly in severity and type, ranging from temporary erythema and urticaria through papular and bullous expression to a dermatitis exfoliativa which resembles that seen from intolerance to the arsphenamins. Itching accompanies all phases of the cutaneous reaction. (7) Hemorrhagic tendency—with hemorrhages into the skin and from the gastrointestinal tract, hemoptysis, epistaxis, hematuria and metrorrhagia.

While mild reactions to gold are quite common, the more severe ones are fortunately rare. Since they occur early in the course of treatment, as a general rule, it is necessary to observe special care at this stage of therapy. An initial dose of 10 mg. is suggested in cases of lupus erythematosus, to be followed at weekly intervals by ascending doses up to 50 mg. In resistant cases the authors suggest a cautious increase of dose to 75 mg. with an upper limit of 100 mg. Numerous authorities attest the equal therapeutic effectiveness of small doses and the incidence of reactions can be greatly lessened by more conservative doses.

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**Cutaneous Calcinosis.**—In reporting a case of calcinosis in a boy, aged 14 years, with multiple calcium tumors on the skin and subcutaneous tissue of the hands, elbows and knees, MALONEY and BLOOM (*Arch. Dermat. and Syph.*, 1931, 23, 245) review the literature of the subject and classify the forms of calcinosis as follows: *A. Local.* This includes calcification in tumors such as epithelioma, atheroma, dermoid cyst and in pseudoxanthoma elasticum. *B. General.* (1) Metastatic calcinosis—associated hypercalcemia from the destruction of bone through

osteomyelitis, caries or lymphatic leukemia. (2) Metabolic calcinosis—an imperfectly understood disturbance of the calcium metabolism unassociated with destruction of bone. The authors stress the frequent association of calcinosis with scleroderma and sclerodactylia. The clinical picture of cutaneous calcinosis consists of small pea to walnut-sized tumors or plaques occurring on the fingers, hands, wrists, elbows and knees often following the course of the tendons. These tumors frequently perforate through the overlying adherent red skin and give rise to a creamy mass often containing small granules. New lesions are apt to appear in crops. Occasionally calcinosis appears as elevated yellow ridges over the elbows and knees.

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## GYNECOLOGY AND OBSTETRICS

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**Operation for Temporary Sterilization.**—In certain cases in which sterilization is indicated it is often desirable that such sterilization be of a temporary nature so that when the indication for the prevention of conception has passed it will be possible to restore the possibility of a future pregnancy. In the usual type of tubal sterilization operation it is quite a difficult matter to restore the continuity of the tube with any degree of assurance as to its future function. The operation which NAUJOKS (*Zentralbl. f. Gynec.*, 1931, 55, 81) describes as a reversible sterilization operation might be of value in such cases. He points out that the operation should not be attempted when there is pelvic inflammatory disease or any marked destruction of the tubal mucosa as in such cases it would be hardly likely that pregnancy would supervene, but in such cases there is seldom an indication for sterilization in the first place. The essential feature of the operation is that the uterine ends of the tubes are not disturbed so that there will be no difficulty later in attempting to anastomose the tubes to the uterus. The operation consists of a crushing of the outer end of the tube with an enterotripter of the Roux type followed by a double ligation of the crushed portion with silk ligatures. The crushing should be evenly distributed across the tube and about 10 mm. wide and with sufficient pressure that there is no doubt that both the musculature and mucous membrane of the tube are actually crushed. This portion of the tube then atrophies into a small cord which is impermeable. When it is desired to restore the patulousness of the tube, it is merely necessary to resect the crushed outer portion, preferably with a diathermy knife so that there shall be no bleeding which might tend to seal the new ostium.



**Results of Olshausen's Operation.**—A review of 3358 cases in which Olshausen's uterine suspension had been performed has been presented by GRAVES and SMITH (*Surg., Gynec. and Obst.*, 1931, 52, 1028) accompanied by an enthusiastic endorsement of the procedure. Of the cases which were followed for more than 2 years symptomatic cures were obtained in 66.8 per cent, relief was obtained in 27.3 per cent while in 5.6 per cent the operation was a failure. From the standpoint of anatomical results, in 76.9 per cent the uterus was in good position, in 14.2 per cent there was a partial recurrence and in 8.8 per cent there was a complete recurrence. Pregnancy occurred 856 times in 489 patients (17.6 per cent of the traced cases) of which 406 had normal deliveries. Abortions and miscarriages occurred in 197 of the pregnancies while the remainder of the pregnancies terminated in some complicated form of delivery, 132 being instrumental. Of the cases examined after childbirth the uterus remained in normal position in 71.4 per cent, there was a partial recurrence in 12.7 per cent and a complete recurrence in 15.7 per cent. The statement is often made that this operation is frequently followed by intestinal obstruction but in this large and carefully followed series of over 3000 cases there were only 6 known cases of intestinal obstruction. Of these 2 died without operation, while of the 4 that were operated upon 3 survived. The above results seem to be most satisfactory especially when it is remembered that the operation was done in over half of the cases for the cure of prolapse and procidentia. (An authoritative review by one of our foremost gynecologic surgeons. C. C. N.)

## RADIOLOGY

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**The Value of the Roentgenologic Examination in Pulmonary Tuberculosis.**—Do changes on the film precede those detected by the usual methods of physical examination? SAMPSON and BROWN (*Am. J. Roent. and Rad. Therap.*, 1931, 25, 209) answer that in a surprisingly large number of cases definite changes characteristic of tuberculosis occur in the film long before definite evidence of abnormal physical signs can be detected. How early in the course of the disease can definite changes be detected? This question the writers do not answer specifically. They point out, however, that in school children they believe roentgenologic evidence of pulmonary tuberculosis exists in many cases for years before symptoms arise that focus attention on the lungs. The incidence of the five cardinal diagnostic data in 1367 cases diagnosed

pulmonary tuberculosis from 1478 consecutive cases in the Trudeau Sanatorium were as follows: Tubercle bacilli, 61.5 per cent; râles, 68.5 per cent; Roentgen ray, +99 per cent; hemoptysis, 33.5 per cent; pleurisy, 12 per cent. The roentgenogram can usually be relied upon to register the extent of the lesion, frequently revealing more disease than is detectable otherwise, and in many instances bringing to light foci which would otherwise be overlooked.

**Palliative Therapy of Malignant Growths.**—That 80 per cent of all persons suffering from cancer are incurable by surgery is the estimate of Wood (*Radiology*, 1931, 16, 291). A few of these patients may be cured, and more can have their lives prolonged over a considerable period of years by radiation. Another group can gain relief from pain and a certain amount of psychic comfort from irradiation, though there be no evidence that life is prolonged. Too much stress has hitherto been laid on the attempt at permanent cure by heavy radiation, which too often renders the patient's life miserable or actually shortens it.

**Roentgenologic Changes in Sarcoid and Related Lesions.**—Boeck's sarcoid, which is characterized by the formation of nodules in the cutaneous and subcutaneous tissues, sometimes associated with fibrocystic changes in the bones or a fibrous infiltration in the lungs, is generally regarded as a form of infection with the bacillus of tuberculosis, although other hypotheses as to its origin have been advanced. KIRKLIN and MORTON (*Radiology*, 1931, 16, 328) have reviewed the roentgenologic observations in 6 cases, of which 2 had demonstrable changes in the bones, 2 in the lungs and 2 in both the bones and the lungs. In the lungs the typical abnormality is a bilateral, fairly dense, diffuse, linear infiltration of the midportion or bases, superimposed on which are discrete opaque areas, ranging in size from miliary nodules to nodules 1 cm. in diameter. The apexes are not affected, and there are no signs of pleurisy or fluid. Of the bones, the phalanges of the hand or foot are most often attacked. The disease of the bone seems to be first evident as a thickening of the trabeculae in the end of the phalanx. Punched-out areas appear and later there is a peculiar combination of destruction and repair. The whole phalanx may be affected. If the process is arrested and healing occurs the bone may return almost to normal, but usually considerable mutilation results.

**Bone Metastasis.**—Three hundred and thirty-four cases of malignant metastasis in bone were studied by COPELAND (*Radiology*, 1931, 16, 198). Of these, 100 cases were consequent on cancer of the breast. The bones most frequently involved in order of incidence were the spine, pelvis, femur, skull, ribs and humerus; metastasis in the forearm and leg was infrequent. The lesions were most often multiple and were single in only one-fourth of the cases. Metastasis occurred in 22 cases of hypernephroma; bones affected, in order of frequency, were the humerus, spine, femur, pelvis, ribs, bones of the feet, skull and sternum. Cancer of the prostate produced metastasis in 134 cases and most frequently involved the pelvis and vertebrae, rarely the femurs, lower end of the tibia and the skull. Malignant disease of the testicle was the primary source in 2 cases, of the bladder in 1, of the ovary in 2 and of the thyroid

in 6. Seven patients with cancer of the stomach had metastasis to the bones, the order being ribs, pelvis and femur, vertebræ, sternum, skull and scapula. Metastasis to bone was found in 4 cases of cancer of the lung; a wide variety of bones were involved, including the lumbar spine, pelvis, ribs and skull.

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**Intravenous Urography.**—BRAASCH (*Am. J. Roent. and Rad. Therap.*, 1931, 25, 196) believes that uroselectan will be only a forerunner to mediums of greater excellence, such as skiodan, which is about to be placed on the market. The author's limited experience with the latter leads him to believe that most of the claims advanced for it are substantiated. Among its advantages are earlier excretion, absence of subjective reaction to its administration and increased clarity of the urograms. It makes available a method which sometimes permits of diagnosis without the necessity of obtaining cystoscopic data. Its universal use will be limited because knowledge of urographic interpretation is necessary and because cystoscopic and other clinical data are usually necessary before exact diagnosis can be made. The greatest value of intravenous urography to the urologist will be its employment in cases in which cystoscopy and ureteral catheterization are contraindicated or impossible. It will be particularly valuable in children. With the present medium the films are still frequently too inexact for interpretation. The greatest weakness of the method lies in its failure to accurately outline minor deformities. Its value will be greatest in the presence of urinary stasis. Failure of renal visualization does not necessarily indicate that renal function has been destroyed. It is frequently of value as a visual functional test and often will suffice to determine the presence of a good kidney on the opposite side from that to which symptoms are referred. Mediums which contain organically combined iodine offer ideal solutions for use in retrograde pyelography.

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**The Effect of Roentgen Rays on the Heart.**—Following up their previous work which tended to show that repeated exposures of the hearts of rats to the Roentgen rays produced definite cardiac lesions, WARTHIN and POHLE (*Am. J. Roent. and Rad. Therap.*, 1931, 25, 625) have endeavored to establish the toleration dose over the precordium of rats. This they found to be 500 r. In cases in which this dose was attained or exceeded no clinical symptoms were observed which might indicate cardiac injury. The only gross pathologic change consisted of a dilatation of the right ventricle. Microscopically, there was Zenker's necrosis in varying degrees, pycnosis of nuclei, and increase in stroma nuclei, with small foci of lymphocytes.

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**Five Years' Experience With Oral Cholecystography.**—After 5 years of daily experience with oral cholecystography, and the use of every known method of administering the dye, STEWART and ILLICK (*Am. J. Roent. and Rad. Therap.*, 1931, 25, 602) still believe that the oral method is the most satisfactory and reliable. If there are any advantages in the intravenous, its very real dangers counterbalance them, and it is not, in the opinion of the writers, a safe office procedure. The oral method is universally applicable and has proved to be entirely reliable. Any dissatisfaction with the Graham test, the writers believe, is due to improper technique.

## NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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**Disseminated Encephalomyelitis.**—GRINKER and BASSOE (*Arch. Neurol. and Psychiat.*, 1931, 25, 723) present, in detail, 4 cases of encephalomyelitis from a clinical and pathologic point of view. They compare these examples with examples of other forms of encephalitis which they have studied, and propose a broad pathologic classification outlining the etiologic conclusions which they feel are justifiable. In Case 1 there was a history of a slight upper respiratory tract infection; five days later there occurred bulbar and cord symptoms, with low-grade fever; death occurred from medullary involvement in nine days. Autopsy revealed multiple perivascular softenings throughout the neuroaxis. In commenting on this case they remark that the entire picture was identical with that which has been described in encephalomyelitis following the use of cowpox vaccine and rabies vaccine, and in encephalitis measles and variola; that "The perivascular, inflammatory, complete and incomplete softenings, with moderate lymphocytic reaction, are typical of these forms of infections;" and ask, "Are all these cases, then, examples of identical virus infections only precipitated by exanthematous disease, vaccinations and nonspecific infections . . . ?" Case 2 was a child in which leg paresis and hemiplegia developed gradually; the opposite leg became involved; stupor developed; a terminal fever led to death in 23 days after the onset. Necropsy revealed a disseminated encephalitis. The extraordinary dissociation of the inflammatory reactions and the patches of demyelination were the high points of interest in this case. The diffuseness of the infiltrations, the character of the cells and their presence distant from the lesions with multiple sclerosis and Schilder's disease would suggest them to be of toxic degenerative origin. Case 3 had severe medullary symptoms, with low-grade fever; there were several remissions over a period of 5 months, then progression with cord symptoms and death. Autopsy showed a subacute disseminated encephalomyelitis. Here the clinical observations indicated clearly that the sites of the lesions were in the brain stem. The nature of the pathologic process was surmised from the suddenness of the onset, the febrile reaction and the relatively rapid course. Case 4 had a previous acute infectious episode, with medullary symptoms. The patient recovered with severe residua; a relapse followed with febrile reaction. In commenting on this case the authors remark that it seems probable that the patient had had an acute disseminated encephalomyelitis, with severe damage to the medulla. The paper continues with a rather vivid discussion of the etiologic factors and the pathologic findings of

the encephalitides in which the authors state that: "The etiologic status of the diffuse encephalitides, including Schilder's disease, has not been solved after many years of pathologic study. No adequate criteria for not considering them infections in origin and searching for their bacterial cause have been advanced by neuropathologists." "The pathologic observations have been typical for all cases. Multiple perivascular lesions are found, particularly about the venules, consisting of complete or incomplete softenings or, in the milder cases or younger areas, demyelination with relatively less axonal destruction. The lesions seem to have a predilection for white matter of both the spinal cord and the cerebrum. A relatively moderate mesodermal reaction in the form of perivascular lymphocytic infiltration has been noted." Still further along they remark: "Thus, it seems that a variety of clinical conditions, including vaccination against smallpox or rabies and exanthematous diseases, such as measles and smallpox in human beings, produce an identical pathologic condition. . . . If a pathologic classification of the central nervous infections were to be proposed on the basis of distinct, regularly occurring microscopic changes, it is apparent that each group would embrace examples of more than one clinical syndrome. Exclusive of syphilis, the parasitic infections and the changes in the brain in sepsis, with its miliary abscesses, such a classification of nonsuppurative encephalitis would be as follows: (1) Severe focal demyelination, less severe axonal damage, microgliosis, mild or absent perivascular lymphocytic infiltration, gliosis (chronic multiple sclerosis and certain cases of acute multiple sclerosis). (2) Focal lesions of incomplete or complete softenings, not perivascular, microgliosis, varying degree of lymphocytic infiltration, vascular proliferation and connective-tissue scar formation (acute disseminated encephalomyelitis and certain cases of acute multiple sclerosis). (3) Focal perivascular incomplete softenings, involving the whole nerve fiber, coalescing of lesions to form softenings, microgliosis, mild lymphocytic reaction, secondary gliosis (cowpox and rabies vaccine, measles, varicella and variola and certain cases of disseminated encephalomyelitis). (4) Diffuse subcortical destruction of nerve fibers, probably beginning in the myelin sheaths, mild or absent lymphocytic infiltration, primary progressive gliosis with secondary regressive glial forms, connective-tissue scar (Schilder's disease and disseminated encephalitis). (5) Diffuse but relatively selective (basal nuclei, medulla or anterior-horn cells) ganglion-cell destruction, abundant perivascular and tissue lymphocytic infiltration, mild microgliosis, white matter spared (rabies, epidemic encephalitis and Heine-Medin's disease). (6) Hyperplastic meningeal reaction, regressive changes in capillary endothelium, formation of new bloodvessels, degenerative changes of ganglion cells, absent mesodermal infiltrations (toxic encephalitis secondary to acute infections and exogenous toxins such as lead).

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**Encephalographic Studies in General Paresis.**—EBAUGH, DIXON, KIENE and ALLEN (*Am. J. Psychiat.*, 1931, 10, 737) report their study of 97 encephalographic studies made upon 70 cases of general paresis. These cases of general paresis they have divided into three groups: (a) Cases that show definite and characteristic findings of mental deterioration—in these cases advanced parenchymatous findings have

occurred; (b) organic reactions with psychoses of functional coloring—this group includes cases of general paresis in which therapy may possibly arrest the pathologic process and restore the patient for either transient or permanent periods—the psychosis simulates the functional disturbances seen in the manic excitements and the depressions as well as other functional reaction types; (c) transitory psychoses without signs of deterioration—this group includes delirious reactions and neurologic irritative phenomena on the basis of exacerbated meningo-vascular and endarteritic disease. The encephalographic studies of the Group A paretics indicated, on the whole, an obliteration of the cortical cerebrospinal fluid pathways, especially in the frontal and parietal areas with dilatation of the basal cisternæ. The authors assume that there has been, apparently, a damming up of the cerebrospinal fluid over the cortex of these areas. (This obliteration of the cortical spinal fluid pathway is known as “arachnoiditis.”) In other cases of this group they found atrophic areas that seemed to be combined with “arachnoiditis.” In still other instances they noted that there was an apparent reduplication of the cortical fluid pathways. In several of these cases marked insular atrophy was found. In the study of the encephalograms of Group B paretics similar findings to these described in Group A were noted. In general, however, they found that the areas of cortical atrophy appeared to be less marked. The “arachnoiditis,” too, was found to be less pronounced. The encephalograms of the paretics grouped under C showed many cortical markings, slight cortical atrophy and very patchy arachnoiditis. In addition to these studies the authors present a comparison of encephalograms before and after nonspecific therapy of general paresis. Here they remark: “The most striking encephalographic pattern shown after malaria therapy consisted in the clearing up of ‘arachnoiditis’ manifest before malaria treatment in 3 cases. The malaria treatment apparently has released the obstructing factor in the cerebrospinal fluid pathways, so that full drainage with wider areas of fluid release has occurred over the cortex.” As a result of this, they find that there is a decrease in the dilatation of the basal cisternæ and further atrophy of the brain is brought into view. They discuss rather adequately the technique of encephalography and the complications encountered, finally concluding that: (1) Encephalography in careful hands is a safe clinical procedure; (2) the encephalographic finding appears to be definitely related to the pathology present in the stage of general paresis studied; (3) clinical improvement and arrest in many of the cases studied appears to be closely correlated with the encephalographic findings present; (4) after sufficient data are collected this method may prove to be of great benefit in further clinical and prognostic groupings of this disease.

#### Some Principles in the Treatment of Behavior Problems in Children.

—LAWSON G. LOWREY (*Arch. Neurol. and Psychiat.*, 931, 25, 884) presents rather briefly the essential points in the treatment of behavior problems of children. He divides the treatment into two parts: (a) direct, and (b) indirect. The direct measures comprise those in which the physician and his assistants deal directly with the patient. The indirect method is defined as the “social-manipulative,” intended to convert the environment of the child into a source of positive rather

than of negative stimuli. In his discussion of the manipulation of the environment he remarks that the measures used may be divided into two major groups: (1) manipulation of things—the adjustment of the environment so that the reaction of the personality to it will be more harmonious, and (2) the manipulation of people—in order that the minimum friction exists between the contacting personalities. In discussing the patient he states that the child is a complicated personality at whatever his stage of development he may be in, that for the creation of an organized personality several points are needed, *viz.*: (a) a satisfaction of a feeling of achievement by the child; (b) recognition by people that he is an individual; (c) affectional relationships with other persons; (d) a feeling of belonging to a group. The author remarks that he and his colleagues have worked out a “new, simple five-fold classification of the common groups of factors involved in the causes of behavior disorders, which is important in focusing treatment.” Group I, the gross mental deviations—psychoses, feeble-mindedness, and epilepsy, and postencephalitic behavior disorders. Group II, gross physical deviations. Group III, the neuroses. Group IV, the complexes and conflicts below the neurotic level. Group V problems, the result of faulty training or ignorance. These groups are discussed adequately, and the paper is concluded with a general outline for a program of treatment of the problems dependent upon the age of the child.

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## PATHOLOGY AND BACTERIOLOGY

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UNDER THE CHARGE OF

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**Selective Distribution of Diphtheria.**—The explanation for the selective infection of certain individuals with *Bacillus diphtheriae* is still far from complete, despite the fact that there have been available to the investigator probably more material facts than for any other infectious disease. Bacteriologic diagnostic methods have improved and have been used extensively for a long time. Toxicity of strains is relatively easy to determine. Antitoxin has been a potent help. The Schick test has added very much to our knowledge and yet there remain many factors about which little is known. It is therefore of great interest and value to have DOULL (*J. Prev. Med.*, 1930, 4, 371) review the present situation of the problems which remain unsettled. He gives as postulates: (1) A case of diphtheria signifies infection overcoming host resistance. (2) Carrier infection with a toxin-producing organism signifies effectual host-resistance. (3) A negative reaction to the Schick test in those untreated and with no history of diphtheria implies

one or more prior subclinical infections. The importance of exposure or dosage is fully discussed as well as that of determined host-resistance in its bearing on age and sex incidence, the infrequency of diphtheria in the negro and in the tropics, and the effect of anatomic factors such as removal of the tonsils. Nevertheless there remain many examples of peculiar local, seasonal and cyclical variations in which the determining factors are obscure, and he suggests that these may be due to the incidence of more pathogenic strains of the bacillus. It is of particular interest that the great pandemic of diphtheria, beginning just after the middle of last century as local epidemics, assumed great malignancy which lasted for twenty or thirty years, after which a decline began, with occasional fluctuations, which has continued to the present.

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**Studies on Inflammation.**—In a series of experiments upon inflammation, MENKIN (*J. Exp. Med.*, 1931, 53, 171) has shown that solutions of ferrie chlorid, trypan blue and horse serum, are more or less fixed at a site of inflammation in rabbits when injected intravenously or directly into the inflamed area. Trypan blue solution injected subcutaneously at the periphery of a superficial area of inflammation did not diffuse into the site of inflammation. The author has demonstrated coagulation or precipitation of horse serum and ferrie chlorid by inflammatory exudates, while normal blood serum did not produce this result. Trypan blue was not affected by such exudates nor by normal blood serum. Histologic study, however, indicated that coagulation or precipitation was a secondary factor in the fixation of foreign substances, the primary agent being mechanical obstruction caused by a network of fibrin about the site of inflammation and by thrombosis of lymphatics. In further studies the author (*J. Exp. Med.*, 1931, 53, 179) showed that in frogs, trypan blue injected into the circulating blood or directly into an area of inflammation was fixed at the inflammatory site. If the dye was injected at the periphery of an inflamed area it failed to enter the site of inflammation. Histologic study again indicated that the failure of diffusion of dye out of or into the inflamed area was the result of occlusion of lymphatic vessels and the presence of a network of fibrin in the inflamed area.

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**Compensatory Hypertrophy of the Adrenal Cortex in the Rabbit.**—In carefully controlled experiments MACKAY and POLLAND (*J. Pathol. and Bacteriol.*, 1931, 34, 73) found that the removal of one adrenal in the rabbit was followed by compensatory hypertrophy of the remaining gland. The hypertrophy was found to be entirely in the cortex. The increase in size evidently took place within the first month since hypertrophy was just as great at the end of 30 days (41 per cent) as at the end of 150 days (37.7 per cent). Compensatory hypertrophy of the adrenal cortex in the rabbit was less in degree than that which followed the removal of one adrenal in the rat.

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**Observations on Melanosis Coli.**—STEWART and HICKMAN (*J. Pathol. and Bacteriol.*, 1931, 34, 61) have made a study of melanosis coli in two series of cases; the first consisted of 600 unselected autopsies at all ages and the second of a consecutive series of 100 cases of carcinoma of the



the animals survive into the chronic stage of the disease than of the controls. The production of tubercular tissue in considerable quantity by injection into the tissues of the phosphatid or liquid saturated fatty acid from the tubercle bacillus does not render the animal allergic, and seems definitely to lower resistance to the disease upon subsequent infection with tuberculosis. The degree to which the tissues react specifically with the formation of new epithelioid cells is indicated by the amount of the change in the M/L index in the blood. The differences observed in individual animals in the amount of tissue reaction to a given amount of phosphatid derived from the tubercle bacillus are definite and are similar to those long noted in connection with humoral antigen-antibody responses with proteins. Both in tuberculosis itself and after intraperitoneal injections of the phosphatid the relation of monocyte to lymphocyte in the blood before death has been a measure of the extent of the epithelioid and lymphoid proliferation found at autopsy. Hence, the M/L ratio can be taken as an index of the relative abundance of these cells in the tissues. Antigenic intravenous doses of the phosphatid itself, or of antiphosphatid serum, given either before or after infection, may give a slight protection to an animal if the dose of infecting organisms be not too great. Taken together, the observations of the present paper implicate the monocyte and its derivative, the epithelioid cell, when harboring living bacilli, as factors in the spread of tuberculosis in the animal. The type of reaction of an animal to the lipoids of the tubercle bacillus, whether predominantly cellular or humoral, may be a decisive factor in determining resistance on the one hand and susceptibility on the other.

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**A Study of Ventilation and Respiratory Illness in New York Schools; Comparison of Window-gravity Ventilation and of Unit Fan Ventilation with Varying Air Flow.**—The original work of the New York Commission on Ventilation called attention to the possibilities of ventilating schoolrooms with a relatively low flow of cool air by the use of window inlets and gravity exhaust ducts. These early studies and those of Greenburg, at New Haven, Childs, at Cleveland, and Butch and Reavis, all suggested that schoolrooms ventilated by the window-gravity method were not only as satisfactory as those ventilated by plenum fans but were actually superior to them—the window-gravity rooms in all four studies showing less respiratory disease among the pupils than did rooms ventilated by fans delivering 30 cubic feet of air per pupil per minute. More recent studies of the New York Commission have, however, brought out very clearly certain possible errors in the use of respiratory disease data as a measure of the healthfulness of the schoolroom. They indicate that not only age and sex but also social and economic status of pupils (as measured by nationality of parents) markedly affect respiratory disease absenteeism; and that respiratory disease in attendance is so affected by subjective judgment that it cannot fairly be used as a criterion if the observations of different observers are compared. On the other hand, results of studies made at Syracuse appear to demonstrate that when age, sex and nationality stock are duly balanced high consistent and significant results may be obtained and that even records of respiratory disease in attendance are concordant when the results are obtained by the same observer. The

present study (*Am. J. Hyg.*, 1931, 13, 235) was designed to check the results in Syracuse in a different city and using unit ventilation instead of a central plenum system for the comparison of air flow and also to compare unit fan ventilation with the window-gravity system (which was not represented in Syracuse). As in the Syracuse studies, it appears that when school populations are balanced as to age, sex and nationality stock, and when the personal equation of the observer is held balanced, concordant and consistent results may be obtained from a study of school absenteeism and of respiratory illness among pupils in attendance. A study of the health of pupils in schoolrooms ventilated by unit ventilators shows that reducing the rate of air flow from the standard figure of 30 cubic feet per pupil per minute to approximately one-half that amount was not attended by any harmful effects so far as could be observed. The teachers preferred the rooms with low air flow on account of freedom from drafts and the lessened noise of the unit motors. A comparison of schoolrooms ventilated with unit ventilators and of those ventilated by window inlets with gravity exhaust shows that the simpler gravity process is quite as satisfactory from the health standpoint as is the system involving the use of fans.

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**Ultraviolet Radiation and Resistance to Infection: Intranasal Infection With the Pneumococcus and With Bacterium Lepisepticum in the Rabbit.**—HARDY and CHAPMAN (*Am. J. Hyg.*, 1931, 13, 255) performed a series of experiments to test the effect of ultraviolet radiation on the resistance of rabbits to pneumococcus Type I and Bacterium leipsepticum infections. It is possible that the rabbit is a poor animal for experiments of this type, as its rapid rise in temperature in direct sunlight makes it probable that the animal never receives any considerable amount of ultraviolet radiation under normal circumstances. The radiation was given several times a week over a period of many weeks before inoculation, and the dose was varied from a suberythral level to a heavy dose causing a severe burn. The average results of five experiments with artificial ultraviolet radiation from a mercury arc and intranasal inoculation with the pneumococcus showed no difference in attack rate or mortality rate between the irradiated group and the controls. Blood count determinations showed no definite difference in the leukocytic reactions of the irradiated and control groups among animals escaping infection. The irradiated animals contracting the disease showed a slightly higher and more rapid leukocytosis than did the infected controls, with a less marked decrease in lymphocytes. The average of three experiments with exposure to direct sun or north sky light through vitaglass showed that both the percentage of infection and the mortality rate after inoculation with pneumococcus Type I was higher in the irradiated animals than that in a control group kept inside. Similar experiments performed with mercury arc radiation and infection with Bacterium leipsepticum showed that radiation had no effect on the susceptibility to infection, although the mortality rate was somewhat lower in the irradiated group. A variation in the amount of ultraviolet, from a marginal erythema to a heavy but subulcerating dose, had no correlation with resistance to the respiratory infections used. The effect of radiation on antibody formation was also investigated. In the pneumococcus infec-

tion experiments the average complement-fixation titer for the irradiated rabbits was slightly higher than for the controls; but in the *Bacterium lepi-septicum* experiments the average titer for the two groups was precisely the same. There was no relation between the titer and the amount of radiation given. In rabbits immunized with killed pneumococci radiation did not accelerate the production of antibodies or increase the amount above the normal.

**Water-borne Typhoid Fever Still a Menace.**—WOLMAN and GORMAN (*Am. J. Pub. Health*, 1931, 21, 115) state that while the typhoid fever death rate in the United States and Canada has made a phenomenal drop since 1900, many large water-borne typhoid outbreaks have occurred during the last decade. Special attention is needed for better control over the safety of water supplies in small cities, as 64.9 per cent of the outbreaks in the United States and 77.5 per cent of those in Canada occurred in those of 5000 population and under. A study of the causes of 282 outbreaks shows clearly the need for more attention on the part of water works and health officials to supervision and control over treatment processes, especially over disinfection where pollutional loads on treatment plants are high or where chlorination is the only safeguard. Over three-quarters of the water-borne illness reported in the United States during the decade 1920-1929, representing 40 per cent of the outbreaks, was due primarily not to pollution of the raw water at its source, but to defects in the system for collecting, treating, storing or distributing of the water for public consumption. Unprotected cross-connections between polluted fire supplies and public water systems were the most important single cause contributing to water-borne outbreaks during the decade 1920-1929 and demand the most active attention of health and water-works officials. During the decade there were 5 repeat water-borne outbreaks in one city from the same cause, and repeat outbreaks in four from different causes. The courts in both the United States and Canada are increasingly holding cities and water companies liable for heavy financial damages for illness resulting from pollution of public supplies.

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ORIGINAL ARTICLES.

THE EFFECT OF PYRODIN POISONING ON THE BLOOD  
AND HEMOLYTOPOIETIC SYSTEM.

WITH ESPECIAL REFERENCE TO THE FORMATION OF HEINZ-EHRlich  
BODIES IN VIVO AND VITRO.\*

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PYRODIN (acetylphenylhydrazin) was brought to the attention of the medical profession in the last decade of the nineteenth century and its therapeutic action as an antipyretic was rather highly recommended. A number of physicians noticed, however, that, although it reduced fever in their patients, a very marked degree

EDITORIAL NOTE.—This and the following 4 papers were presented at the 23d annual meeting of the Undergraduate Medical Association of the University of Pennsylvania, based on work performed by the student authors read at that time during the free and elective hours of their curriculum. Three of the other 8 articles ("An Anaphylactic Response of the Nongravid Uterus of the Unanesthetized Rabbit," by G. L. Weinstein, '33; "The Progress of Undergraduate Research in Medical Schools" (third study) by M. P. Foley, '31, and J. N. Marquis, '31; and "The Use of Caesium Tetraiodophenolphthalein in Cholecystography," by Julian Johnson, '31) were also considered worthy of publication; but the last named is being held for further experiments, while arrangements have already been made to publish the other two, in *Science* and the *American Journal of Physiology*, respectively. Not only are these 8 articles well worth publication for their intrinsic merit, but also it is thought that the appearance of the 5 as a group will give some deserved recognition to work done often under considerable difficulty and presented under circumstances which are believed to be unique in the medical schools of this country.

E. B. K.

\* Awarded the Mary Ellis Bell first prize at the Twenty-third Annual Meeting of the Undergraduate Medical Association of the University of Pennsylvania, May, 1931.

of anemia resulted from its administration. For this reason the compound fell into disrepute and little was heard of it for a matter of 15 to 20 years, except for its use by a few investigators for the study of experimental anemia in animals. Within the past 20 years, however, the phenylhydrazin derivatives have come into vogue for the treatment of plethoric conditions, most particularly polycythemia vera, the hydrochlorid being the most used drug of the group.

Since Krumbhaar<sup>1</sup> (1929), in a study of experimental anemia produced by pyrodin, noted the appearance of round, refractile, eosinophilic bodies within erythrocytes, falling in the group of the so-called Heinz-Ehrlich bodies (hemoglobinämische Innenkörper, Glasskörper), the hemotoxic action of the phenylhydrazin group has been the source of interest in this laboratory.

The literature holds a number of observations of these "Innenkörper." They occur only in severe toxic anemias, notably those induced by exotoxins, such as phenylhydrazin derivatives, toluylendiamin, anilin dyes, potassium chlorate, nitrobenzol, pyrogallie acid and others. Recently Zadek and Burg<sup>2</sup> (1930) reported a series of 3 cases in which these pathologic forms were observed in the blood.

No completely satisfactory work has been done to demonstrate the exact mechanism of the formation of these bodies, in an attempt to explain the hemolytic action of the agents producing them. Some authors have thought of a nuclear origin, others a mitochondrial (on account of their reaction to Janus green); Schilling<sup>3</sup> states definitely "Alle diese Körper sind nicht karyogen, sondern archoplasmatisch," but attempts to establish a structural basis for them in the "capsular body" and "microcenter" of his anatomic scheme of the erythrocyte. As will be shown later, our work *in vitro* confirms the former statement, but fails to show ground for the latter.

Waddell, Wolff and Lanou,<sup>4</sup> (1930), working in this laboratory, presented evidence to show that pyrodin acted directly on the mature red blood cell, and suggested that a reaction between the drug and hemoglobin took place within the cell. This reaction resulted in the formation of small, dense, refractile aggregations of an insoluble methemoglobin-like compound. (Fig. 1.)\* As the action of the drug on the individual cell persisted, these intracellular bodies grew somewhat larger and the cell outline remained as a ghost, finally completely disintegrating and leaving the bodies free in the blood stream, whence they were phagocytized by cells of the reticuloendothelial system. They noted, too, the avidity of

\* Previous workers, considering the question from a chemical aspect, have shown that the phenylhydrazin compounds are strong reducing agents and split the hemoglobin into its pigment and protein fractions. The basic drug becomes oxidized, setting free a benzol ring which is the active agent in blood destruction.

these latter cells for erythrocytes, both visibly intact and in various stages of degeneration. They were able to reproduce the intracellular bodies by the action of pyrodin on dog blood *in vitro*, but

TABLE 1.—RABBIT BLOOD FINDINGS IN PYRODIN POISONING.

	Date.	Dose.	Pyrodin (EKC).	Pyrodin (E and A).		Phenylhydr. HCl.	
			No. 1.*	No. 2.	No. 3.	No. 4	No. 5.
R B C (in millions)	1/7/31	0	6.26	7.09	6.26	6.14	6.35
Hemoglobin			.97	.99	.91	1.03	1.02
R B C (in millions)	1/8/31	0	6.87	6.91	7.02	6.69	7.01
Hemoglobin			.88	1.00	.95	1.00	.91
	1/9/31	(A)					
R B C (in millions)	1/10/31	(B)	6.68	6.61	7.01	6.29	6.20
Hemoglobin			.91	.98	.97	1.00	.96
R B C (in millions)	1/12/31		4.26	4.73	4.27	4.30	4.45
Hemoglobin			.66	.77	.65	.75	.72
R B C (in millions)	1/13/31	(C)	3.28	4.14	3.75	4.61	4.62
Hemoglobin			.49	.51	.51	.65	.64
R B C (in millions)	1/14/31		3.26	3.14	3.14	3.71	4.56
Hemoglobin			.49	.46	.48	.55	.65
R B C (in millions)	1/15/31		2.76	2.90	2.48	3.83	4.47
Hemoglobin			.48	.43	.42	.46	.62
R B C (in millions)	1/16/31	(D)	2.59	2.94	2.21	3.29	4.46
Hemoglobin			.53	.52	.47	.53	.64
R B C (in millions)	1/17/31		2.70	2.33	2.16	3.14	3.94
Hemoglobin			.41	.40	.38	.45	.55
R B C (in millions)	1/18/31		2.55	1.97	2.02	3.04	3.74
Hemoglobin			.42	.38	.37	.48	.58
R B C (in millions)	1/19/31		2.61	2.72	2.13	2.67	3.42
Hemoglobin			.54(E)	.52(E)	.50	.53(F)	.51
R B C (in millions)	1/20/31		2.45	2.45	2.32	2.45	2.56
Hemoglobin			.47	.48	.45	.45	.44
R B C (in millions)	1/21/31		3.21	2.22	1.81	2.61	2.31
Hemoglobin			.43	.35(?)	.43	.40	.41
R B C (in millions)	1/22/31		1.76	2.33	2.49	2.50	2.07
Hemoglobin			.52	.51	.48	.44	.45
R B C (in millions)	1/23/31		3.37	3.31	2.86	2.59	2.47
Hemoglobin			.67	.61	.60	.60	.58

Hemoglobin is expressed as 1.0 equaling 100 per cent Sahli.

(A)  $\frac{1}{2}$  cc. of each drug subcutaneously; (B) 1 cc. of each drug subcutaneously; (C)  $1\frac{1}{2}$  cc. of each drug subcutaneously; (D) 3 cc. of each drug subcutaneously; (E) 4 cc. of Pyrodin subcutaneously; (F) 4 cc. of Phenylhydrazin hydrochlorid subcutaneously.

\* The other rabbit in this subgroup became unsuitable for continued testing.

did not observe the reaction during its course, merely noting the end results in stained smears.

**Experiments.** The work reported here was planned to confirm and further the latter studies. The action of both pyrodin and phenylhydrazin hydrochlorid has been observed on the blood and hemolytopoietic system of the dog and rabbit, and, in addition, their effect on the dog and human erythrocyte has been studied in hanging-drop preparations, so that the reaction has been followed from beginning to end.

Six rabbits composed the first experimental group. These were subdivided into three groups of two. To the first of the subgroups, pyrodin of Eastman make was administered subcutaneously, beginning with a dose of  $\frac{1}{2}$  cc. of a 1 per cent solution; to the second, pyrodin of Eimer and Amend make was given similarly in the same dose; to the third group, phenylhydrazin hydrochlorid was given, using the same dose and like technique. Anemia was to be prolonged, so that successive doses of the drugs were necessarily increased, as an acquired tolerance was rapidly established in each case. The later doses are indicated in Table 1.

Two dogs constituted the second group, to each of which were given 2 cc. of a 2 per cent solution of pyrodin (Eimer and Amend) per kilogram of body weight, subcutaneously. This was repeated 2 days later, and the blood of the animals was studied throughout the consequent anemic period until the counts returned to normal. After a short interval one of the dogs received a second course of the drug to demonstrate acquired tolerance, if present. The appended tables show the course of the blood determinations.

**Action on the Blood. Rabbit.** In these animals anemia appeared on the second day following injection and reached its maximum on the third day. Without further injection the counts rose from this point. Succeeding administration of the drugs before the blood counts rose produced a progressively increasing anemia. A striking tolerance was noted. It was necessary to increase the dosage with each injection in order that the downhill trend in the blood counts might be maintained; for example, in the case of pyrodin, the first injection in 1 rabbit was  $\frac{1}{2}$  cc. of a  $\frac{3}{4}$  per cent solution and was followed by a drop in the red cell count of about 3.8 million and 32 per cent hemoglobin, while in the same animal the fifth injection with 8 times that amount resulted in a drop of but 420,000 red cells and 7 per cent hemoglobin.

The effect of both drugs was essentially the same, the pyrodin, however, proving the more potent. Using the average counts, the latter drug produced in rabbits a diminution of the red cell count from 6 to 2.1 million on the eleventh day, while the rabbits receiving the same dosage of phenylhydrazin hydrochlorid had an average count of 3.3 million on the eleventh day.

Stained smears of the blood were made daily to determine the condition of the individual erythrocytes. There seemed to be no striking difference in the red cells of any of the groups. In each case the erythrocytes showed a "motheaten" and vacuolated appearance on the third day after the first injection. The round, refractile, darkly staining intracellular bodies, the so-called "inner bodies," appeared the following day, at which time the red count varied between 3 and 4 million. Anisocytosis, poikilocytosis and polychromatophilia and an occasional nucleated red cell were noted at this time. These latter changes, indicating the outpouring of young cells from an overactive bone marrow, were present throughout the

anemic period, the erythroblastic forms increasing in number as the anemia proceeded. At the end of 2 weeks, when the erythrocyte

TABLE 2.—DOG BLOOD FINDINGS IN PYRODIN POISONING.

	Day.	Dog No. 1.	Dog No. 2.	Dose, Dog No. 1.	Dose, Dog No. 2.
R B C (in millions)*	1*	8.68	7.39		
Hemoglobin		1.18	.95		
R B C (in millions)	2	8.28	7.10	24 cc. 2% Pyrodin	24 cc. 2% Pyrodin
Hemoglobin		1.09	.92		
R B C (in millions)	3	7.65			
Hemoglobin		1.02			
R B C (in millions)	4	7.09	5.98	24 cc. 2% Pyrodin	24 cc. 2% Pyrodin
Hemoglobin		1.04	.90		
R B C (in millions)	5	7.81	5.13		
Hemoglobin		1.00	.90		
R B C (in millions)	6	6.46			
Hemoglobin		.80			
R B C (in millions)	7	....	4.36		
Hemoglobin		....	.65		
R B C (in millions)	8	3.54	2.57		
Hemoglobin		.45	.43		
R B C (in millions)	9	2.50	1.73		
Hemoglobin		.40	.30		
R B C (in millions)	10	1.90	2.43		
Hemoglobin		.32	.30		
R B C (in millions)	11	2.18	2.36		
Hemoglobin		.40	.42		
R B C (in millions)	12	2.00	2.80		
Hemoglobin		.40	.52		
R B C (in millions)	13	2.90			
Hemoglobin		.40			
R B C (in millions)	14	....	3.62		
Hemoglobin		....	.60		
R B C (in millions)	15	3.16	3.77		
Hemoglobin		.50	.58		
R B C (in millions)	16	3.70	3.74		
Hemoglobin		.58	.53		
R B C (in millions)	17	3.50	3.96		
Hemoglobin		.65	.61		
R B C (in millions)	18	3.70	4.60		
Hemoglobin		.66	.65		
R B C (in millions)	19	4.30			
Hemoglobin		.72			
R B C (in millions)	20	3.65			
Hemoglobin		.65			
R B C (in millions)	21				
Hemoglobin					
R B C (in millions)	22	5.04	5.18		
Hemoglobin		.80	.70		
R B C (in millions)	23	4.89			
Hemoglobin		.75			
R B C (in millions)	24	4.93			
Hemoglobin		.72			
R B C (in millions)	26	5.33			
Hemoglobin		.81			

\* Normal.

Hemoglobin is expressed as 1.0 equaling 100 per cent Sahli.



counts averaged slightly over 2 million and the hemoglobin 40 per cent, injections of the drugs were discontinued, and 2 days later, when the counts in each case showed a beginning recovery, autopsies were performed on all the animals except No. 4. The tissues from lung, liver, spleen, lymph node, adrenal, kidney and femoral bone marrow were removed, fixed in Zenker-formol, sectioned and examined. The surviving animal was maintained in an anemic state for 4 more weeks before autopsy was performed.

*Dog.* The range of the erythrocyte and hemoglobin values is shown in Table 2. From a normal of 8.7 million and 118 per cent, Dog 1 showed a fall to 1.9 million and 32 per cent on the tenth day. Similarly Dog 2 dropped from 7.5 million and 95 per cent to 1.7 million and 30 per cent on the ninth day. The second week after injection showed both animals maintaining erythrocyte counts of between 2 and 3 million, after which the blood picture improved, and at the end of 3 weeks each showed a count of over 5 million and appeared perfectly healthy. After a rest period of 1 week 1 of the dogs was subjected to a second series of injections of pyrodin. The dosage which had produced previously such a profound anemia in this dog now was far less potent. The red cell count dropped to but 3.77 million and the hemoglobin to 50 per cent, the animal showing no objective symptoms of anemia. This is regarded as striking proof of a rapidly acquired tolerance to pyrodin.

The daily blood smears showed changes similar to those described for the rabbits, the intracellular bodies appearing even more clear-cut in the dog blood, as shown in Fig. 1. They persisted until the blood counts approached normal, becoming gradually less in number as recovery proceeded. More detailed description of these bodies will be given in the account of the studies *in vitro*.

*Action on the Hemopoietic System. Rabbit.* Fig. 2 is typical of the diffuse hyperplasia seen in the bone marrow of all of the animals. Practically all of the fat has been replaced by hemopoietic elements. Cells of the erythroblastic type are far in excess of those of the granulocytic series—the ratio being approximately 10 to 1. The other tissues removed at autopsy were carefully searched for evidence of myeloid metaplasia and positive finds were made in several instances. Fig. 3 showed a sharply circumscribed area of metaplasia in the adrenal cortex. In another case the metaplastic focus was more diffuse. In both of these areas erythroblasts of early and late forms and young granulocytes were found. The spleens of several of the rabbits showed similar areas of myeloid metaplasia of rather diffuse character. The cells of these latter blood-forming islands were confined to the erythroblastic type. (Fig. 4.) The liver of 1 of the animals showed a number of megakaryocytes scattered singly throughout the section. Their position in the sinusoids suggested metaplasia rather than colonization from the blood stream. (Fig. 5.) The young forms of blood cells, both medullary and extra-

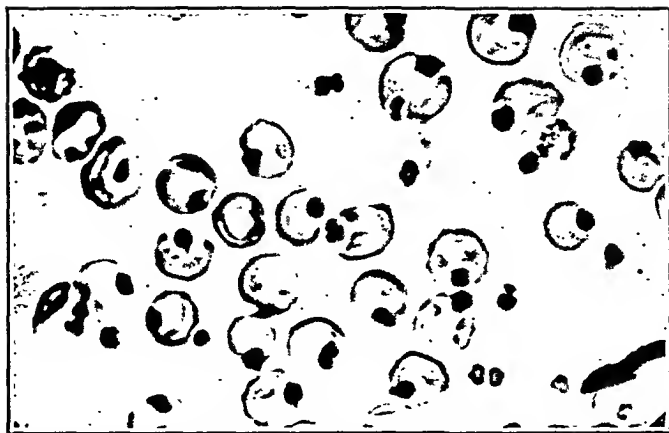


FIG. 1.—Stained smear of dog blood showing Heinz-Ehrlich bodies within erythrocytes and free in plasma.  $\times 1150$ .

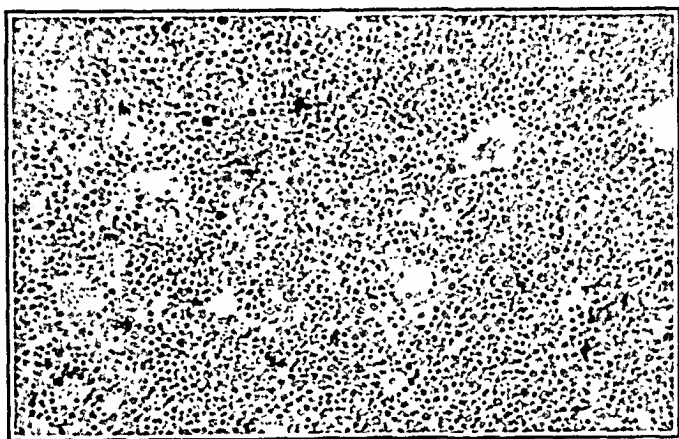


FIG. 2.—Bone marrow (Rabbit). Extreme hyperplasia (chiefly erythropoietic.)  $\times 120$ .

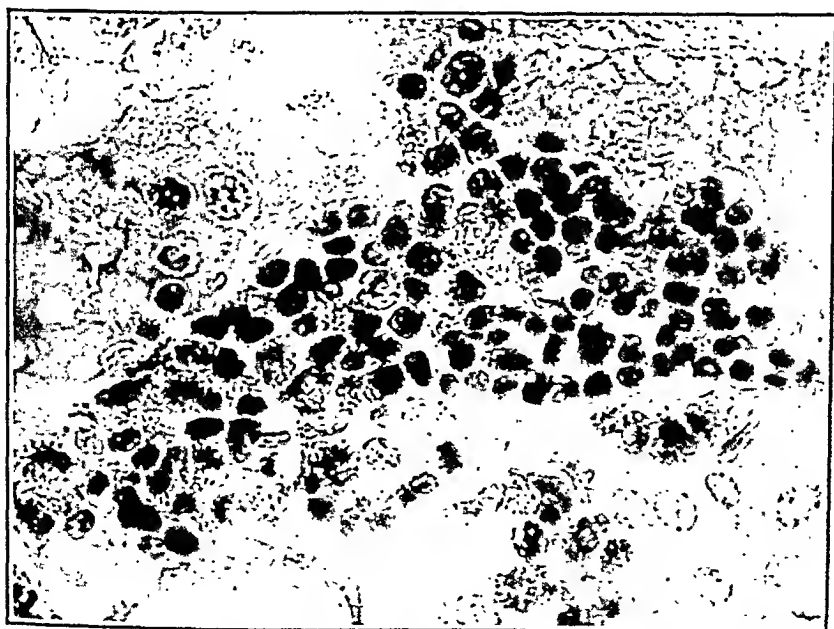


FIG. 3.—Adrenal cortex (Rabbit). Focal myeloid metaplasia. (Immature cells of both series, but mostly erythroblasts.)  $\times 630$ .

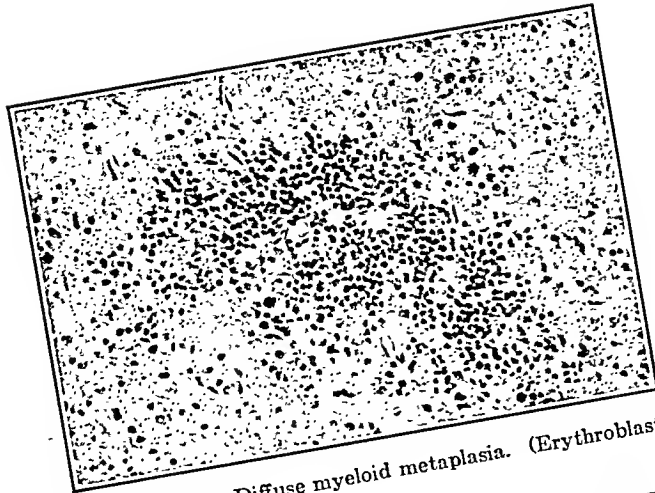


FIG. 4.—Spleen (Rabbit). Diffuse myeloid metaplasia. (Erythroblastic.)  $\times 175$ .

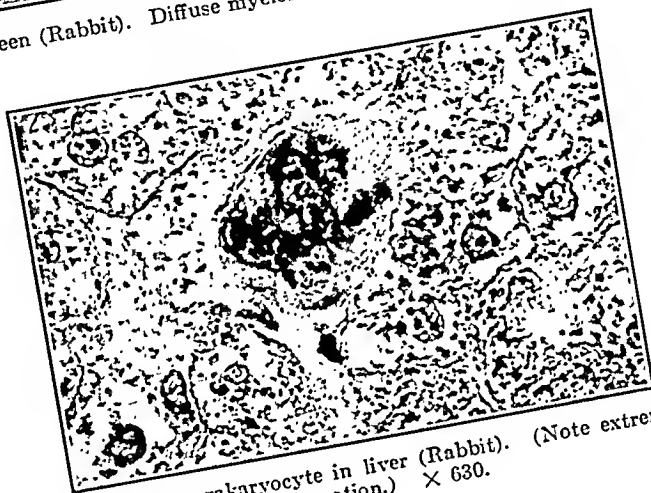


FIG. 5.—Metaplastic megakaryocyte in liver (Rabbit). (Note extreme liver cell degeneration.)  $\times 630$ .

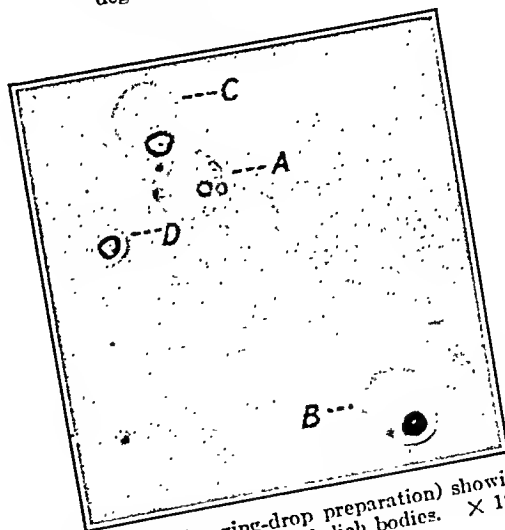


FIG. 6.—Pyrodon dog blood (hanging-drop preparation) showing various stages in the formation of Heinz-Ehrlich bodies.  $\times 1200$ .

medullary, showed no evidences of degenerative effect from the hemolytic agent.

*Dog.* Through the medium of repeated biopsy of the femoral bone marrow, Waddell, Wolff and Lanou demonstrated the rapid and progressive hyperplasia of this tissue in the face of increasing anemia, beginning at the margin of the myeloid cavity and extending toward the center, until the normal fat of the marrow had been practically completely replaced by hemopoietic tissue. Careful examination of the cellular elements showed no evidence of degeneration, indicating that the pyrodin did not injure the blood-forming organs *per se*. Their work and results were so clear cut that it was not felt necessary to repeat this phase.

**Action on the Hemolytic System.** *Rabbit.* The sections from all the organs showed a marked response of the cells of this system, especially in the bone marrow and spleen. The so-called reticular cells of the former tissue were markedly increased in number and were filled with both blood pigment and red blood cells in various stages of degeneration. The spleen showed a great hyperplasia of reticuloendothelial cells, and in each case contained a massive amount of hemosiderin, both intracellularly and extracellularly. The lymph nodes and liver presented a similar picture, but to a lesser degree.

*Dog.* Phagocytosis of degenerated red cells and blood pigment in a similar fashion has been demonstrated by Waddell, Wolff and Lanou.

**Action on the Parenchyma of Viscera.** A distinct toxic action of these drugs was observed on the parenchymal elements of the various viscera, particularly marked in the liver and kidney. Fig. 5 illustrates the tremendous degeneration of the liver cells which follows the repeated administration of the phenylhydrazin derivatives. The kidney showed degenerative changes in both glomeruli and tubular epithelium, and in 1 case a quite pronounced round-cell infiltration. These observations suggest cautious administration of the drugs therapeutically.

**Action in Vitro.** *Dog and Human Blood.* Previous experimentation has shown that the end result of the action of pyrodin on the erythrocyte *in vivo* and *in vitro* is quite the same. The experiments noted here were designed to demonstrate this reaction step by step *in vitro*, so that the exact hemotoxic mechanism might be better understood. It was soon found that the dog and human erythrocyte reacted identically; hence, no attempt is made to report individual experiments. The evidence presented is a compend of the ensemble gained from study of many preparations of both types, the human blood cells having been used in most cases.

Weak dilutions of erythrocytes suspended in an isotonic saline solution were mixed in a red blood cell pipette with various dilutions of pyrodin, and hanging-drop preparations were made, sealed and

examined, using the oil-immersion objective. These preliminary measures were carried out to determine at what concentration the reaction was sufficiently gradual to permit observation under the microscope. When this optimum point was found (equal parts of a 1 to 100 dilution of red blood cells in physiologic salt solution and a 1 per cent solution of pyrodin, (Eimer and Amend)) the findings noted below were seen. It had been thought that vital staining with brilliant cresyl blue would facilitate the observations, due to a preferential affinity for the "inner bodies." It was found, however, that the reaction could be followed with as much ease in the unstained preparations; hence this procedure was discarded.

Primarily there is a slight crenation of the erythrocyte until the drug enters the cell. Within a minute, however, osmotic equilibrium is established and the normal round cell-contour returns. Next, an opaque shadow appears within the erythrocyte, occupying about  $\frac{1}{4}$  of the flat surface area, irregular in shape and having a rather hazy outline. This shadow-like body becomes sharper of outline, more opaque and smaller (to about  $\frac{1}{6}$  the diameter of the cell), then increases in translucency and refractility, finally looking almost vacuole-like. A given cell may contain 1 or more of these seeming vacuoles. Cell A in Fig. 6 contains 3 such structures and suggestions of 4 more. These "vacuoles" move about freely within the cell but never escape beyond the limiting cell membrane. Further observation often shows a fusion of the "vacuoles" and always a slow fading of the color of the erythrocyte, through the stages of Cells B, C and D in Fig. 6. The latter is the so-called "ghost cell," consisting of a persisting cell membrane, and within its circumference the "inner body" and otherwise invisible material. Ghost cells are seen frequently in contact with an adjacent cell at the point where the inner body is attached (as Cell C to Cell A in Fig. 6), probably a surface-tension phenomenon. It is for this reason that previous observers, from the study of stained smears, have conceived the idea that these bodies are merely fragments of erythrocytes destroyed by the drug through rhesis, attached to intact cells and that they are not formed intracellularly. Fig. 6 in itself disproves this idea. Finally, the persisting cell membrane of the ghost cell completely disintegrates and the inner bodies are left free in the suspension.

**Summary and Conclusions.** 1. Acetylphenylhydrazin and phenylhydrazin hydrochlorid each produce profound anemia when injected subcutaneously into experimental animals, the action being identical in the dog and rabbit.

2. Acetylphenylhydrazin is more potent than the hydrochlorid in its anemia-producing effect.

3. A marked tolerance to each drug is rapidly acquired by the animals.

4. Both drugs are toxic, in that they produce degenerative changes in the parenchyma of the viscera, extremely pronounced in the liver and kidney.

5. Neither drug produces visible degenerative changes in immature blood cells. There is a rapid and extreme hyperplasia of the bone marrow, and in some cases an appearance of myeloid metaplasia in the adrenal, spleen and liver.

6. There is marked activity of the hemolytic system, characterized by hyperplasia of reticular and sinusoidal endothelial cells and pronounced phagocytosis of degenerated erythrocytes and blood pigment by these elements.

7. Dense refractile bodies appear within the erythrocytes concomitant with the appearance of the anemia and are present throughout its course.

8. These intracellular bodies are formed within the erythrocyte. There is an apparent primary condensation reaction between the drug and hemoglobin, followed by formation of semifluid bodies which fuse and become semisolid, concomitant with a fading of hemoglobin within the cell. The cell membrane is the last structure to undergo disintegration, finally leaving the "inner body" free in the blood stream.

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### THE INFLUENCE OF ULTRAVIOLET LIGHT ON PLASMA CLOT FORMATION.\*

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CATTLE blood plasma, as is well known, upon coagulation forms a dense, white clot, which is very opaque. In sterilizing blood plasma by means of ultraviolet light, one of us (Vogelaar) observed that

\* A portion of this paper was presented by the junior author at the Twenty-third Annual Meeting of the Undergraduate Medical Association for which it received the John G. Clark Founder's Prize.

citrated blood plasma, irradiated for several hours with ultraviolet light, forms a transparent clot upon the addition of a solution containing calcium chloride.

The mechanism of the clotting process in normal mammalian blood as revealed by the ultramicroscope has been studied by Hekma,<sup>1</sup> Howell,<sup>2</sup> Stübel,<sup>3</sup> and many others. They all agree that during coagulation a large number of sharply defined fibrin needles appear and form an irregular meshwork. Hekma, in particular, has demonstrated that the fibrin needles are made up by the aggregation of smaller units which he has called elongated points (*längliche Punkte*). According to this author, the fibrin needles and threads occasionally appear spontaneously in the fluid without any indication of their formation by the previous aggregation of smaller particles. In the majority of cases, however, the elongated points (*längliche Punkte*) form the fibrin needles and these, in their turn, the fibrin threads. The fibrin needles can arrange themselves side by side or end on end and these two processes explain the increase of the fibrin threads in width and length.

**Methods.** Blood was obtained at the slaughter house from animals (bovine) killed by bleeding from the neck. Twenty cc. of an 8.3 per cent sodium citrate solution were added to 500 cc. of blood to prevent coagulation. To secure plasma, 100-cc. samples of the blood were centrifuged for one-half hour at a speed of approximately 3000 revolutions per minute and a radius of 19.5 cm. One half cc. amounts of this plasma were pipetted into small glass tubes (2.5 cm. high; 1 cm. in diameter) and covered with a quartz plate in order to prevent evaporation of the plasma. The tubes were placed directly beneath a "Hanovia Sun Alpine lamp" (table model) so that the mercury arc was 32.5 cm. above the plasma. Irradiation was carried out at room temperature over a period of 4 hours. Several of the tubes were removed every hour, so that samples of plasma were obtained which had been irradiated with ultraviolet light for 1, 2, 3, and 4 hours.

A series of 5 pyrex test tubes, each containing 0.5 cc. of Calcium Ringer solution\* was next prepared. To the first test tube was added 0.5 cc. of normal cattle plasma and this was used as a control tube. To the other 4 tubes was added 0.5 cc. of plasma irradiated respectively for 1, 2, 3, and 4 hours. The contents of these tubes were thoroughly mixed and allowed to clot.

Fig. 1 shows the results of this experiment. It may be seen that the clot in the control tube (*i.e.* test tube No. 1) is very opaque, whereas the clot of the plasma irradiated for 4 hours with ultraviolet light is quite transparent (*cf.* test tube No. 5). It may also be observed that there is a gradual, but marked increase in the transparency of the clots proportional to the increase in irradiation

\* Calcium Ringer solution contains per 100 cc. of H<sub>2</sub>O: 0.95 gm. NaCl, 0.2 gm. KCl, 3.6 gm. CaCl<sub>2</sub>.

time. This effect was found experimentally to reach a maximum at 4 hours' irradiation and after that time (up to 12 hours' irradiation) no further visible changes occurred in the clots.

The plasma was then examined through the ultramicroscope, using the test-tube experiments to control the microscopic observations. Plasma was prepared according to the described method and a drop of the mixture placed in a dark-field chamber (Leitz) and allowed to clot. This chamber is constructed on the same principle as a blood-counting chamber so that a uniform depth is always obtained. The chamber was cleaned with soap and water, stored in cleaning solution for 24 hours and washed in water, alcohol and ether. Immediately before using it was coated with collodion, which was allowed to dry and was then stripped off. This procedure gave a nearly optically empty glass surface. Further details as to cleaning glassware may be found in Gage's article.<sup>4</sup>

An optical bench equipped with a 30-ampère direct current carbon arc lamp was used. The microscope was fitted with the special dark-field apparatus designed by Spierer.<sup>5,6</sup> In making the photographs a Leitz Makam camera was used in conjunction with Eastman 33 photographic plates.

**Observations.** The dark-field picture of blood plasma is remarkable. A great mass of highly refractile, white fibrin needles distributed in a uniform manner are visible, while scattered about are numerous bright centers of more closely packed needles. The individual needles are clear-cut, brilliant and distinct. In the spaces between the needles, bright particles are seen dancing about in active Brownian movement, while still others are entangled and are either motionless or only slightly vibrating. These are the chylomicrons of Gage and Fish,<sup>7</sup> the significance of which has been discussed by these authors and by Ludlum and his coworkers.<sup>8</sup> Fig. 2 shows a clot obtained from untreated blood plasma. Fig. 3 represents plasma which has been irradiated with ultraviolet light for 1 hour. There is very little difference between this picture and that of untreated plasma. In Fig. 3a, several of the so-called centers of fibrin formation are shown.

In the sample of plasma which has been irradiated for 2 hours, however, the first changes brought about by the ultraviolet light are seen. The microscopic field presents a rather dense, uniform fibrin formation with the usual centers, somewhat similar to that observed in the untreated and 1-hour samples. Closer observation of the fibrin needles discloses several changes, the most outstanding of which is the decrease in distinctness and brilliancy. The needles have lost their clear-cut outlines and appear as hazy structures. Also conspicuous is the tendency of the needles to assume a thread-like appearance with a slight wavering of the needle outline.

The sample of plasma irradiated for 3 hours and reproduced in Fig. 4, shows a progressive intensification of the changes previously



described. There is a dull and indistinct fibrin network with the delicate thread-like needles forming a more or less coarse cloth.

There is a marked difference between the clot obtained from untreated plasma and that from plasma irradiated for 4 hours with ultraviolet light. In Fig. 5, no fibrin needles can be seen, and the plasma clot appears as a gelatinous mass. That there is a clot, however, may be demonstrated in various ways. The characteristic clot structure may be observed under the low power of an ordinary microscope, or again one can lift the clot out of the dark-field chamber.

In these experiments, a gradual change was observed from the distinct, brilliant needles of the untreated plasma clot through stages of increasing dullness, blurring of the needle outlines, and the assumption of an almost thread-like appearance, to the final stage after 4 hours' irradiation, where no fibrin needles were visible and the clot was optically structureless.

**Discussion.** These observations were repeated in a series of 32 experiments and the changes described were constant. An interesting fact was brought out by comparing the test-tube clots with the microscopic pictures. The change in transparency in the test-tube clots took place gradually, regularly and apparently in proportion to the time of irradiation. Thus up to 4 hours' exposure, the greater the irradiation time the greater is the increase in the transparency of the clot. In 17 experiments, the microscopic pictures showed little change until the end of 3 hours' irradiation after which time there was a rather sudden alteration in the appearance of the fibrin needles. Table 1 illustrates this.

TABLE 1.—CORRELATION OF MACROSCOPIC AND MICROSCOPIC OBSERVATIONS.

Experiment No.	Clot in 3-hour tube.	Fibrin needles in 3-hour dark-field preparation.	Experiment No.	Clot in 3-hour tube.	Fibrin needles in 3-hour dark-field preparation.
1 . . . . .	T	—	17 . . . . .	T	+
2 . . . . .	O	+	18 . . . . .	T	+
3 . . . . .	T	+	19 . . . . .	T	+
4 . . . . .	T	+	20 . . . . .	T	+
5 . . . . .	T	+	21 . . . . .	T	+
6 . . . . .	T	—	22 . . . . .	T	—
7 . . . . .	T	—	23 . . . . .	T	+
8 . . . . .	T	—	24 . . . . .	T	—
9 . . . . .	T	—	25 . . . . .	T	—
10 . . . . .	T	—	26 . . . . .	T	+
11 . . . . .	T	+	27 . . . . .	T	—
12 . . . . .	?	?	28 . . . . .	T	+
13 . . . . .	T	+	29 . . . . .	T	+
14 . . . . .	OT	?	30 . . . . .	T	+
15 . . . . .	?	?	31 . . . . .	T	+
16 . . . . .	T	—	32 . . . . .	T	—

T = transparent clot; O = opaque clot; — = absence of fibrin needles in dark-field pictures; + = presence of fibrin needles in dark-field pictures; ? = no data available.

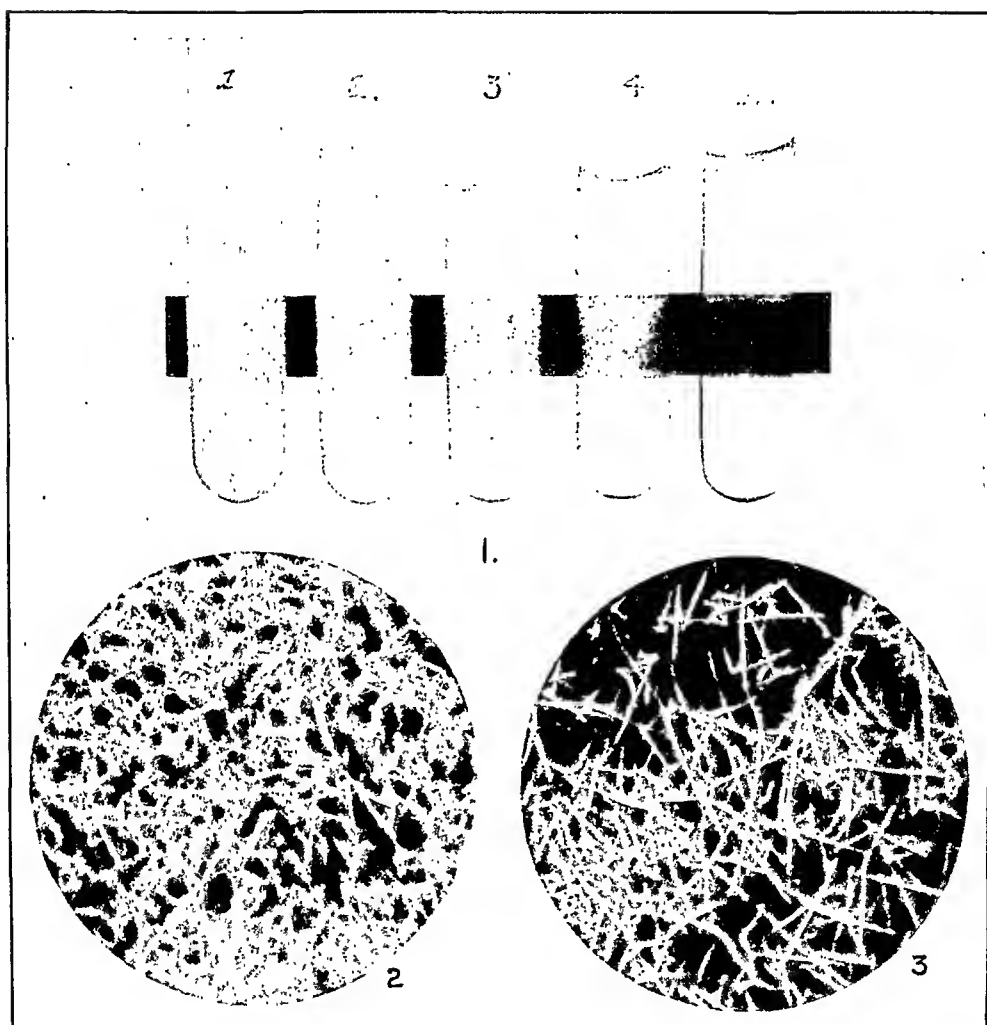
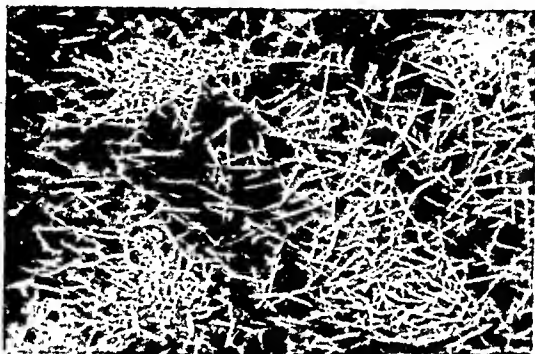


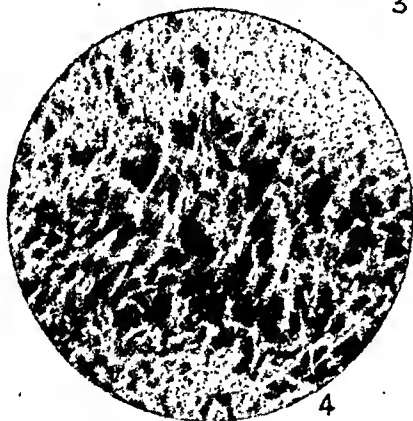
FIG. 1.—Test tubes showing change in transparency of plasma clot resulting from blood plasma progressively irradiated by ultraviolet light. No. 1 tube control and others 1, 2, 3 and 4 hours' radiation.

FIG. 2.—Photomicrograph of normal blood plasma clot.

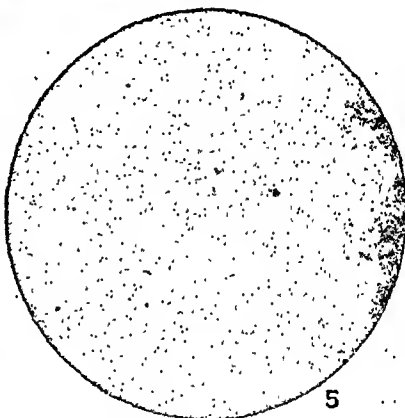
FIG. 3.—Photomicrograph of a clot of blood plasma previously irradiated for 1 hour with ultraviolet light.



3 A



4



5

FIG. 3a.—Photomicrograph of a clot of blood plasma previously irradiated for 1 hour with ultraviolet light and showing centers of fibrin formation.

FIG. 4.—Photomicrograph of a clot of blood plasma previously irradiated for 3 hours with ultraviolet light.

FIG. 5.—Photomicrograph of a clot of blood plasma previously irradiated for 4 hours with ultraviolet light.

The influence of ultraviolet light on blood plasma is not clearly understood at present, but the following explanation of our observations is suggested. The opacity of the clot obtained from the untreated plasma depends upon the fact that it is a heterogeneous system, the different phases of which have different indices of refraction. It is this difference in refractive index between the fibrin needles and the serum which makes the needles visible. A change in the index of refraction of the different parts of any heterogeneous system may have a great influence on the transparency of the whole system (*cf.* the Spalteholz method of preparing transparent bone specimens). Such a change may occur in our experiments. Thus the fibrin precursor (fibrinogen) of the plasma may be so altered under the influence of ultraviolet light that, upon forming fibrin, it takes up an excess quantity of water. The result of this process is a change in the index of refraction of both the fibrin and the continuous phase (serum), so that the transparency of the system as a whole is increased. It will be readily understood, that when the indices of refraction of both phases have become equal a maximum degree of transparency is reached. Assuming that under the influence of ultraviolet light the above mentioned changes occur, the system may change to the opaque state when irradiated for a longer time than is necessary to secure an entirely transparent clot. This will, of course, happen when the index of refraction of the fibrin needles becomes lower than that of the serum. In this case, the reaction will give an optimum degree of transparency after a certain length of time. A longer or shorter treatment will result in a clot that is less transparent. It was in only two instances, however, that the clot seemed to become less transparent with an increase in the irradiation time. In all other cases a maximum degree of transparency was obtained after 4 or 5 hours of treatment and longer exposure to the ultraviolet rays resulted in no further apparent changes.

**Summary.** 1. There is a gradual increase in the transparency of a clot formed by calcifying citrated blood plasma which has been irradiated with ultraviolet light from 1 to 4 hours.

2. These changes have been demonstrated both macroscopically and microscopically.

3. The suggestion is made that they are due to an imbibition of water by the fibrinogen when it forms fibrin. This process results in an alteration of the index of refraction of the different parts of the system with a consequent effect on the transparency of the system.

**NOTE.**—We take pleasure in expressing our thanks to Prof. William Seifriz for his advice and to Miss Helen Brevoort for technical assistance.

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## THE BLOOD SUGAR RESPONSE TO EPINEPHRIN IN THYROID-FED ANIMALS.\*

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BURN and Marks<sup>1</sup> have reported that when rabbits are fed thyroid preparations there is at first an increased hyperglycemic response to epinephrin injections, and at this period of thyroid feeding there was found on chemical determination to be no decrease in the glycogen content of the liver. Later in thyroid feeding there resulted a greatly decreased hyperglycemic response to epinephrin, and at this time there was a marked depletion of liver glycogen. Marks,<sup>11</sup> in a later study primarily concerned with the effect of glucose injections in thyroid-fed rabbits made the statement that: "The injection of 0.5 mg. adrenalin into a rabbit in the advanced stage of thyroid feeding usually by itself brings on a fatal hypoglycemia in a short time. Whether or not this is preceded by a detectable hyperglycemia depends on the completeness with which the glycogen reserves have been exhausted."

This fall in blood sugar after epinephrin when the liver glycogen is decreased is a phenomenon of considerable theoretical interest. The first question that arises is whether this hypoglycemia may be due to the stimulation of the islands of Langerhans. Would this hypoglycemia occur after the removal of the pancreas in an "acute" experiment under amytal anesthesia?

It was to answer this question that the following experiments were carried out. The rabbit, being an unsuitable animal for pancreatectomy, it was thought advisable to use the dog. However, before experiments were begun on the dog the experiments of Burn and Marks, and Marks were repeated in 1 rabbit to secure the proper control of experimental conditions.

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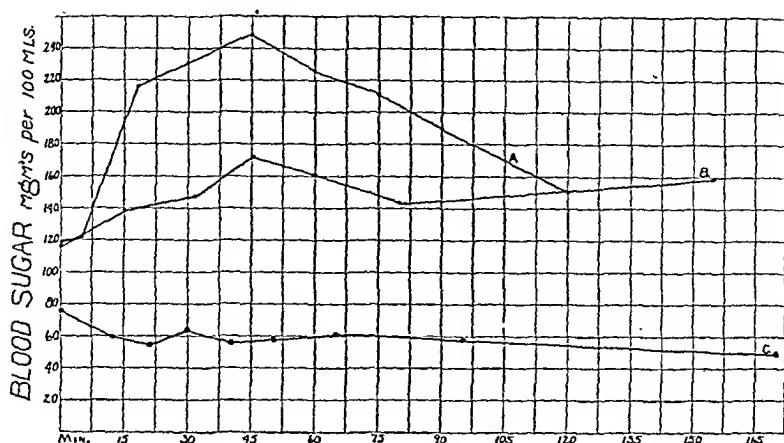
It is to be emphasized that our experiments are concerned with the late stages of excessive thyroid feeding. It is well known that thyroid feeding in animals increases the sensitiveness of the sympathetic nervous system and greatly increases the various effects of epinephrin. As a result, it is to be expected that so long as there is abundant liver glycogen, there will be increased glycogenolysis resulting from epinephrin injections and increased hyperglycemia. It was only after prolonged thyroid feeding in rabbits that Burn and Marks found the liver glycogen reduced and an absence of epinephrin hyperglycemia, and our attempts to produce such a state in other animals are recorded in the following experiments.

**Experimental Procedure.** The desiccated thyroid used represented five times its weight of fresh thyroid gland. The epinephrin used was the 1 to 1000 solution of adrenalin chlorid of Parke, Davis & Co. Blood sugar determinations were made by the Jensen and Hagedorn method. The animals were fed the normal diet on the afternoon of each day. No food was given on the day that a blood sugar curve was carried out. Amytal anesthesia was used in some of the experiments, as indicated in the protocols.

RABBIT 1.			
Date.		Body weight, kilos.	Thyroid, gm.
Oct. 17, 1930	Curve A:	epinephrin, 0.45 cc. intravenously	
Oct. 17		2.78	0.2
Oct. 20		2.52	0.2
Oct. 21		2.64	0.1
Oct. 22		2.52	0.2
Oct. 23		epinephrin, 0.4 cc. intravenously	
Oct. 23		2.52	0.2
Oct. 24		2.42	0.2
Oct. 27		2.22	0.2
Oct. 28		2.40	0.1
Oct. 29		2.22	0.2
Oct. 30	Curve B:	epinephrin, 0.4 cc. intravenously	
Oct. 30		2.16	
Oct. 31		...	0.2
Nov. 1		...	0.25
Nov. 3		2.14	0.1
Nov. 4		2.16	0.2
Nov. 5		2.00	0.2
Nov. 6	Curve C:	epinephrin, 0.4 cc. intravenously	
Nov. 6		1.80      Died	

Curves A, B and C (Chart I) show a progressive decrease in the hyperglycemic response to the injection of epinephrin, which suggests a gradual diminution in the amount of liver glycogen, on the basis of Burn and Marks' work. Curve C shows an actual fall rather than a rise in blood sugar. The animal passed into a moribund state. Intravenous injection of glucose was given in an attempt to save the animal, but it immediately became convulsive. It was killed with ether. The data are summarized in Table 1.

Epinephrin caused an increase in the rate of respiration and prostration, and although asphyxia probably complicated the last Curve C no rise in blood sugar occurred.



A, October 17, 1930, 0.45 cc., Adrenalin 1 to 1000

B, October 30, 1930, 0.40 cc., Adrenalin 1 to 1000

C, November 4, 1930, 0.40 cc., Adrenalin 1 to 1000

CHART I.—Blood sugar curves after epinephrin injection in Rabbit 1 before and after thyroid feeding.

TABLE 1.

	Curve.	Days of thyroid feeding.	Total amount of thyroid, gm.	Epinephrin injected, cc.	Initial level of blood sugar, mg.	Highest level of blood sugar, mg.	Rise, mg.	Rise, per cent.
Rabbit 48 . . .	A	0	...	0.45*	119	248	129	108.0
	B	14	1.60	0.40*	117	172	55	47.5
	C	21	2.55	0.40*	76	49	-27	-28.9
Cat 1 . . . .	A	5	12.0	1.00†	171	292	121	70.8
	B	15	31.0	0.60†	112	221	109	97.3
Cat 2 . . . .	A	20	51.0	0.40†	94	149	55	58.4
	B	35	82.0	0.40†	99	208	109	110.1
Cat 3 . . . .	A	13	40.0	0.40*	118	196	78	66.1
	B	27	70.0	0.40*	92	143	51	55.4
Dog 1 (No. 414)	A	0	...	0.50*	106	187	81	76.4
	B	0	...	2.00†	105	226	121	115.2
	C	29	78.0	1.50†	118	203	85	72.0
	D	36	120.0	1.50†	155	224	69	44.5
	E	42	180.0	{0.50†}	142	188	46	32.4
	F	50	280.0	0.50*	137	168	31	22.6
Dog 2 (No. 620)	A	19	242.0	0.50*	141	179	38	27.0
	B	32	522.0	0.50*	152	220	68	44.6
	C	37	647.0	0.50*	102	147	45	44.1
Dog 3 . . . .	A		0.006†	1.00*	92	134	42	45.6
	B		0.056†	1.50*	140	180	40	28.5

\* Intravenous injection. † Subcutaneous injection. ‡ Phosphorus (gm.).

Having thus reproduced the results of Burn and Marks, and Marks, the same procedure of thyroid feeding and epinephrin blood sugar curves was carried out in dogs. The results follow:

Dog 1 (No. 414). In this dog amytal anesthesia was used in all curves except in Curve B, which was performed as a test for a suitable dosage of epinephrin. The epinephrin was injected either subcutaneously or intravenously and is indicated as such.

Dog 1.		
Date.	Body weight in kilos.	Thyroid gm.
Dec. 4, 1930	8.6	
Dec. 4	Curve A: amytal, 0.56 gm. epinephrin, 0.5 cc. intravenously	
Dec. 11	8.8	
Dec. 11	Curve B: epinephrin, 2.0 cc. subcutaneously	
Dec. 12	8.8	4
Dec. 14	...	4
Dec. 15	...	4
Dec. 16	...	4
Dec. 17	...	4
Dec. 18	8.8	4
Dec. 20	8.6	4
Dec. 22	...	5
Dec. 23	...	4
Dec. 24	...	4
Dec. 26	...	4
Dec. 29		5
Dec. 30	8.2 very nervous	5
Dec. 31	8.2	4
Jan. 2, 1931	8.4	
Jan. 5	...	4
Jan. 6	Excitable and very nervous	5
Jan. 7	8.4	5
Jan. 8	...	5
Jan. 9	...	5
Jan. 10	Curve C: amytal, 0.546 gm. epinephrin, 1.5 cc. subcutaneously	
Jan. 10	8.4	7
Jan. 12	8.2	7
Jan. 13	...	7
Jan. 15	...	7
Jan. 16	...	7
Jan. 17	Curve D: amytal, 0.546 gm. epinephrin, 1.5 cc. subcutaneously	
Jan. 17	9.0	9
Jan. 19	...	7
Jan. 20	...	7
Jan. 21	...	7
Jan. 22	...	10
Jan. 23	...	10
Jan. 24	Curve E: amytal, 0.611 gm. epinephrin, 0.5 cc. intravenously 0.5 cc. subcutaneously	
Jan. 24	9.4	10
Jan. 26	...	20
Jan. 27	...	20
Jan. 28	...	20
Jan. 29	...	20
Jan. 30	...	20
Jan. 31	Curve F: amytal, 0.57 gm. epinephrin, 0.5 cc. intravenously	
Jan. 31	8.8	



In Chart II each curve shows a fairly marked rise in blood sugar, but the response becomes less with the increase in the amount of thyroid ingested. The least response, however, still shows a distinct rise. Curves A and F represent the response to identical doses intravenously. Curves B, C and D indicate the reactions to subcutaneous injections; B is a curve before thyroid feeding was begun, and shows an extreme and prolonged rise in blood sugar; D, after 120 gm. of thyroid, shows a prolonged gradual rise in blood sugar. Curve C is a peculiar response; there is an initial rise, but it is



- A, December 4, 1930, 0.5 cc., Adrenalin 1 to 1000, Intravenously, Amytal Anesthesia  
 B, December 11, 1930, 2.0 cc., Adrenalin 1 to 1000, Subcutaneously  
 C, January 10, 1931, 1.5 cc., Adrenalin 1 to 1000, Subcutaneously, Amytal Anesthesia  
 D, January 17, 1931, 1.5 cc., Adrenalin 1 to 1000, Subcutaneously, Amytal Anesthesia  
 E, January 24, 1931, { 0.5 cc., Adrenalin 1 to 1000 Subcutaneously } Amytal Anesthesia  
                                   { 0.5 cc., Adrenalin 1 to 1000 Intravenously }  
 F, January 31, 1931, 0.5 cc., Adrenalin 1 to 1000, Intravenously, Amytal Anesthesia

CHART II.—Blood sugar curves after epinephrin injection in Dog 1 before and after thyroid feeding.

suddenly interrupted by a sharp drop from 173 to 47 mg. It remained between 47 and 63 mg. for a period of almost 2 hours and then suddenly rose to a value of 203 mg. How much significance is to be attached to this curve is difficult to say, for it never occurred in any of the other experiments. The initial rise shows that the liver was still capable of responding to the epinephrin. The initial blood sugars varied for all of these curves between 100 and 155 mg. of blood sugar. For this we have no explanation; but varying blood sugar levels are common findings in hyperthyroidism. Table 1 summarizes the data.

In Curves C, D, E and F there was probably edema of the lungs, as there was a certain amount of frothing and difficulty in respiration. This was probably due to the increased sensitiveness to adrenalin in the hyperthyroid state. The dog was in good condition following the experiment but was cyanotic at times during the experiment.

## Dog 2.

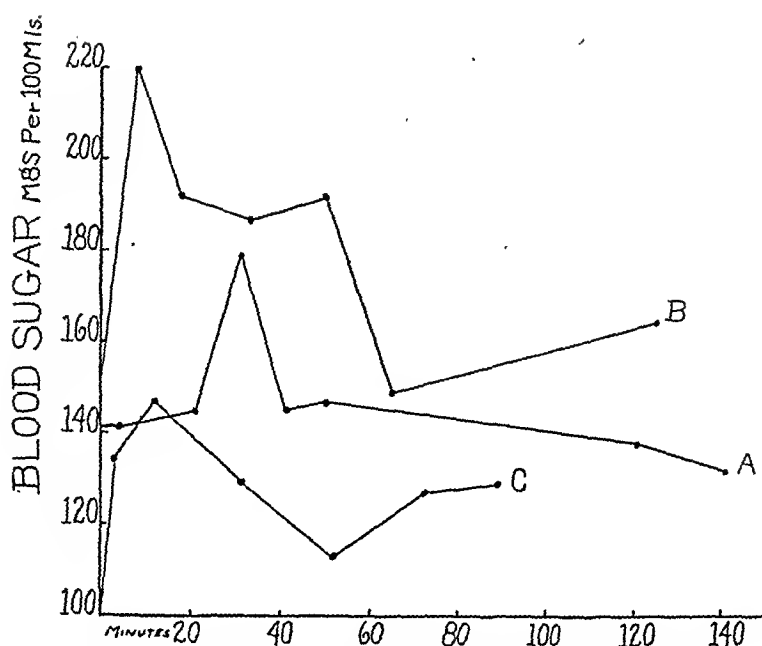
No amytal anesthesia was used.

Date.	Body weight, kilos.	Thyroid, gm.
Feb. 16, 1931	8.10	15
Feb. 17	...	15
Feb. 19	...	17
Feb. 20	...	15
Feb. 21	...	20
Feb. 24	7.8	20
Feb. 25	8.25	20
Feb. 26	8.20	20
Feb. 27	8.10	20
Feb. 28	8.09	10
Mar. 2	7.80	10
Mar. 3	8.00	20
Mar. 5	...	10
Mar. 6	8.20	
Mar. 6	Curve A: epinephrin, 0.5 cc. intravenously	
Mar. 7	...	20
Mar. 8	8.00	20
Mar. 9	8.00	20
Mar. 10	8.00	20
Mar. 11	8.15	20
Mar. 12	...	20
Mar. 13	...	20
Mar. 14	...	20
Mar. 16	8.05	20
Mar. 17	8.20	25
Mar. 18	8.15	25
Mar. 19	...	25
Mar. 20	Curve B: epinephrin, 0.5 cc. intravenously	
Mar. 20	...	25
Mar. 21	...	25
Mar. 22	...	25
Mar. 23	...	25
Mar. 24	...	25
Mar. 25	...	25
Mar. 26	Curve C: epinephrin, 0.5 cc. intravenously	

This dog was in good condition at the close of the experiment in spite of the fact that he had been fed such large doses of thyroid. Chart III illustrates the blood sugar curves and Table 1 summarizes the findings.

All of the curves in Chart III show a distinct increase in the blood sugar following the injection of the epinephrin. The rise is more sudden after the feeding of thyroid than before.

The results of these 2 dogs showed that under the conditions of the experiments thyroid feeding did not lead to an absence of the hyperglycemic response to epinephrin.



A, March 6, 1931, 0.5 cc., 1 to 1000 Adrenalin Intravenously

B, March 20, 1931, 0.5 cc., 1 to 1000 Adrenalin Intravenously

C, March 26, 1931, 0.5 cc., 1 to 1000 Adrenalin Intravenously

CHART III.—Blood sugar curves after epinephrin in Dog 2 at various times during thyroid feeding.

**Dog 3. Effect of Phosphorus Poisoning.** A dog was then administered phosphorus subcutaneously, when it was expected that the liver injury from such poisoning would reduce the glycogen store.

**Dog 3.**

Date.	Blood sugar, mg.	Phosphorus mg.
Jan. 26, 1931	103	2
Jan. 27	105	2
Jan. 28	115	2
Jan. 29	113	..
Jan. 31	92	..
Curve A: 1 cc. epinephrin, intravenously		
Feb. 2	119	4
Feb. 3	...	4
Feb. 4	99	4
Feb. 7	86	4
Feb. 11	136	4
Feb. 12	...	4
Feb. 13	138	..
Feb. 14	...	4
Feb. 19	99	2
Feb. 20	94	..
Feb. 21	...	4
Feb. 24	...	6
Feb. 27	140	10
Curve B: 1.5 cc. epinephrin, intravenously		
Mar. 1	Dog died	

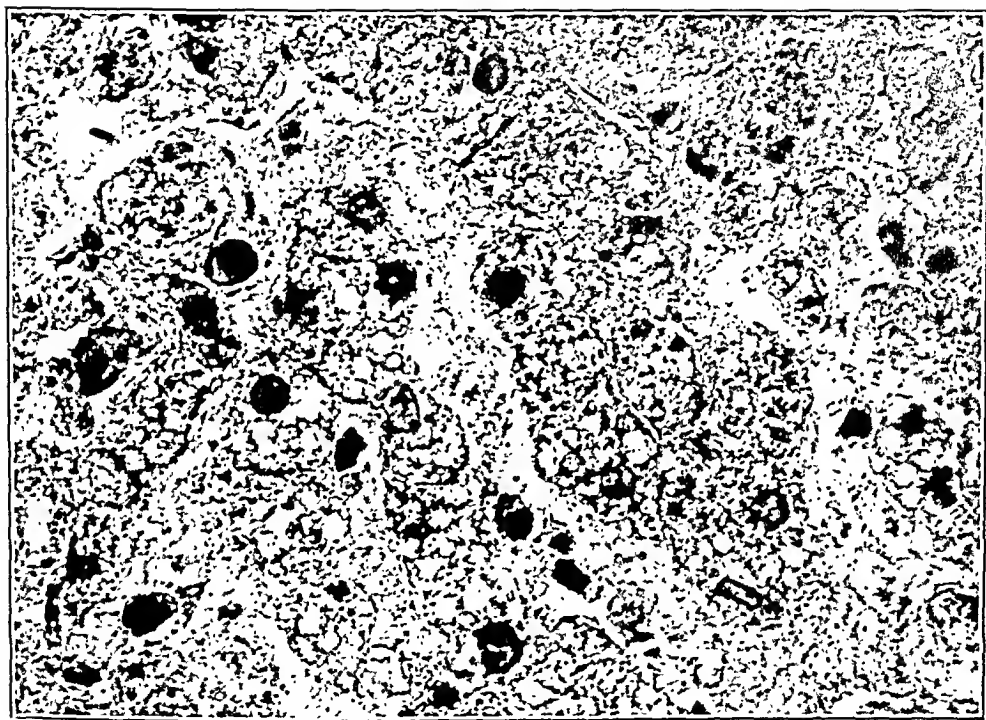
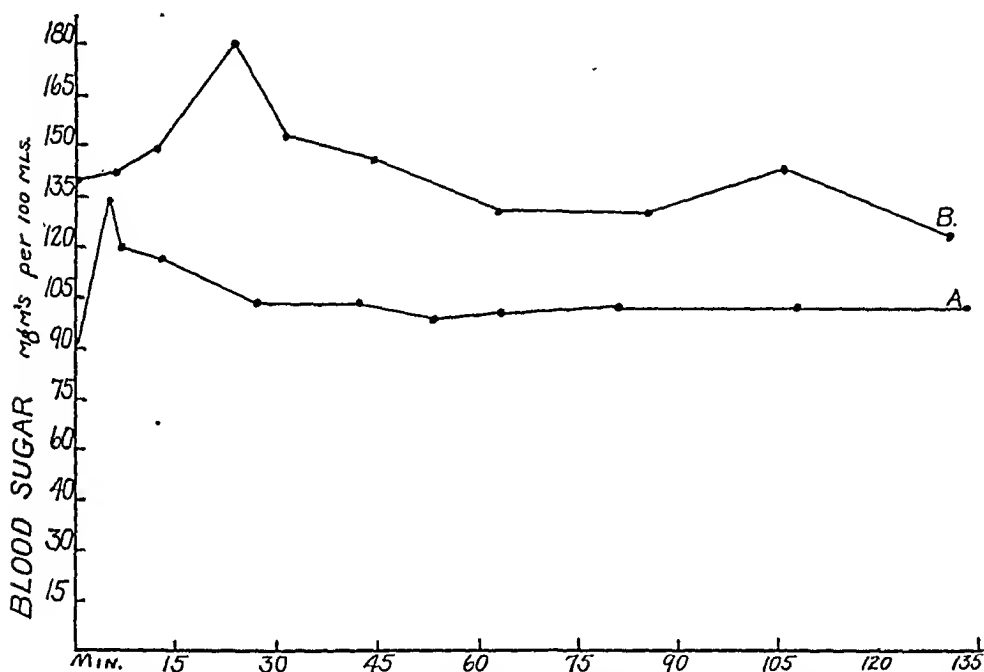


FIG. 1.—Photomicrograph of liver of dog poisoned with phosphorus, showing severe injury.



The dog used was a large shepherd, male, weighing 20.5 kilos. Yellow phosphorus was emulsified in olive oil and injected subcutaneously. Epinephrin was injected into the femoral vein in both curves.

The dog was very sick during the last few days of his life, and frequently vomited his food. Chart IV represents the graphic record of his blood sugar response. The summary is given in Table 1.



A, January 31, 1931, 1.0 cc. of 1 to 1000 Adrenalin Intravenously

B, February 27, 1931, 1.5 cc. of 1 to 1000 Adrenalin Intravenously

CHART IV.—Blood sugar curves after epinephrin in Dog 3 poisoned by phosphorus.

Curves A and B in Chart IV show an increase in the blood sugar of approximately the same magnitude. The reaction was more delayed after the phosphorus had had time to act. There had been some food given to the dog by mistake before Curve B, but it was vomited.

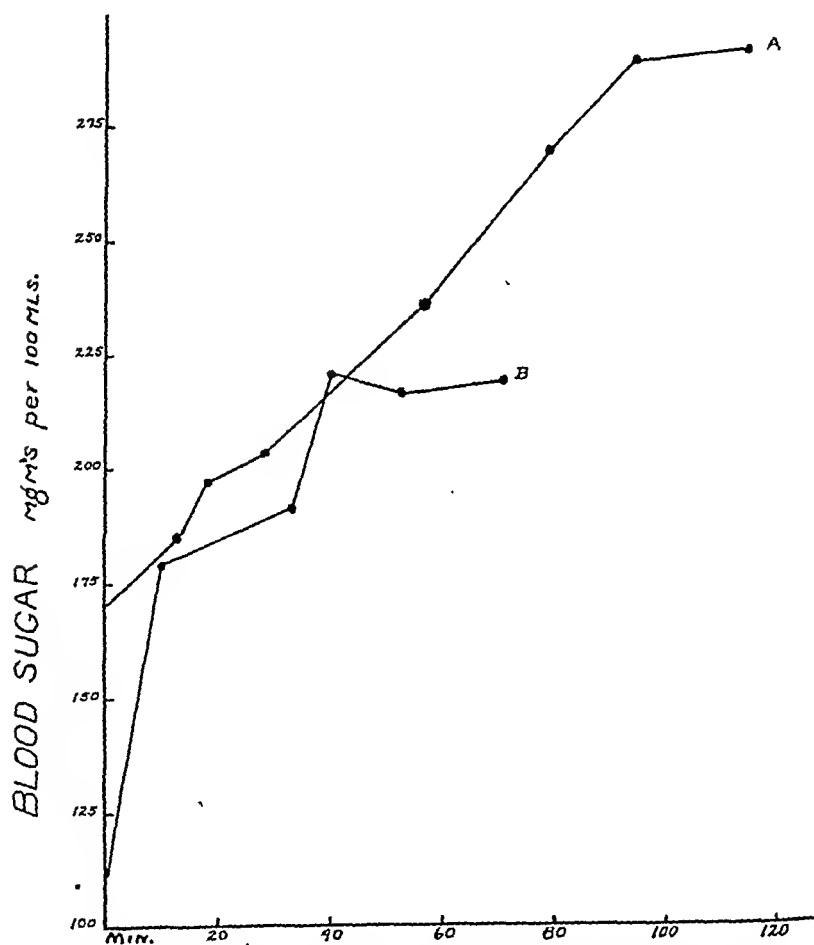
This experiment indicates that even in fatal phosphorus poisoning epinephrin led to hyperglycemia. The photomicrograph of the liver (Fig. 1) indicates the severe injury to the liver.

Since it seemed impractical to carry thyroid feeding in dogs to a point where the conditions found in the rabbit could be duplicated, the cat was next tried. The results follow:

CAT 1. The cat was a female, weighing 2.8 kilos. The epinephrin was injected subcutaneously after 50 mg. of amytal per kilo had been injected intraperitoneally and complete anesthesia had been induced.

## CAT 1.

Date.	Body weight, kilos.	Thyroid, gm.
Feb. 21, 1931	2.8	5
Feb. 24	...	3
Feb. 25	2.4	4
Feb. 26	...	4
Feb. 27	Curve A: epinephrin, 1 cc. subcutaneously	
Feb. 28	...	3
Mar. 2	...	3
Mar. 3	2.0	3
Mar. 4	...	3
Mar. 5	1.9	3
Mar. 6	1.9	3
Mar. 6	Curve B: epinephrin, 0.6 cc. subcutaneously	
Mar. 7	Cat died	



A, February 27, 1931, 1.0 cc., 1 to 1000 Adrenalin Subcutaneously

B, March 6, 1931, 0.6 cc., 1 to 1000 Adrenalin Subcutaneously

CHART V.—Blood sugar curves after epinephrin injection in Cat 1 during thyroid feeding.

Both the curves (Chart V) show a similar rise in blood sugar over the fasting level. There is only 1 mg. difference in the extent of the reaction. However, it is to be noted that the fasting level for Curve A is much higher than that for Curve B.

Fifteen hours after Curve B was run the animal was found in convulsions. The blood sugar at this time was 115 mg., which shows that the convulsions were not due to hypoglycemia. An autopsy was performed but no significant lesions were found either grossly or histologically.

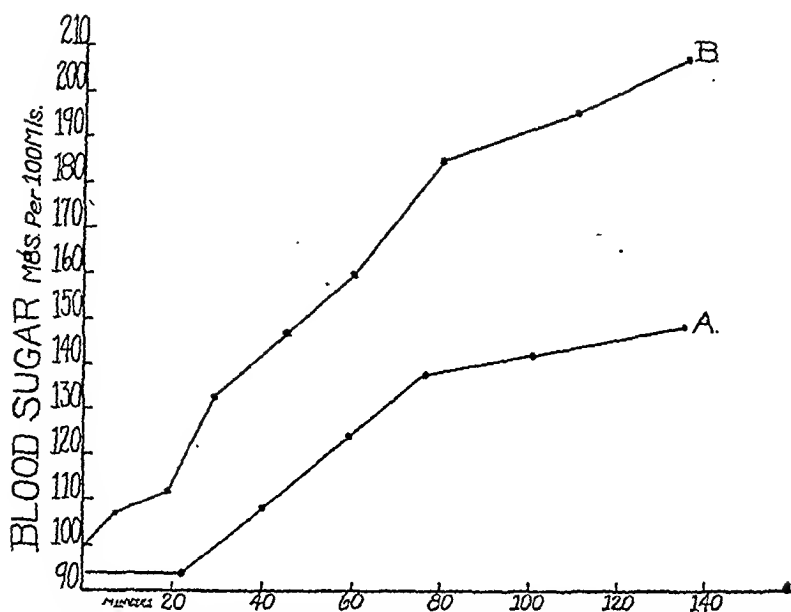
The rapid loss of weight which this animal showed was thought at first to be due to the thyroid feeding, but later it became apparent that the animal was suffering from some spontaneous pathologic condition.

CAT 2. The epinephrin was injected subcutaneously; amytal anesthesia was used; the dose and method of injection were the same as that used in Cat 1. The amytal injection was made about 1 hour and 15 minutes prior to the taking of the first blood sample. The weight of the cat and the doses of thyroid are given in the following table:

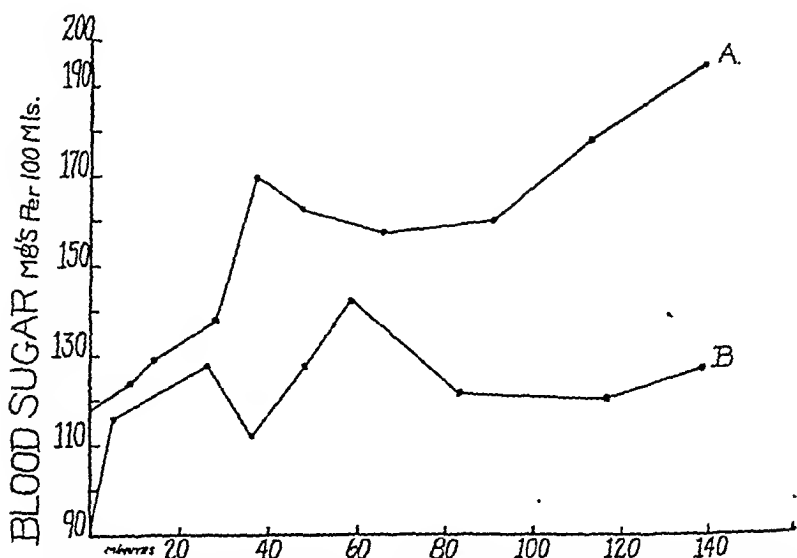
Date.	Body weight, kilos.	Thyroid, gm.
Mar. 7, 1931	2.60	3
Mar. 9	2.55	2
Mar. 10	2.45	2
Mar. 11	2.55	2
Mar. 12	2.45	2
Mar. 13	...	2
Mar. 14	...	2
Mar. 16	2.22	3
Mar. 17	2.20	3
Mar. 18	2.25	3
Mar. 19	...	3
Mar. 20	...	3
Mar. 21	...	4
Mar. 22	...	3
Mar. 24	...	4
Mar. 25	2.15	5
Mar. 26	...	4
Mar. 27	Curve A: epinephrin, 0.4 cc. subcutaneously	
Mar. 28	...	5
Mar. 30	...	5
Mar. 31	...	4
April 1	...	3
April 2	1.90	3
April 3	...	3
April 4	...	3
April 6	1.70	3
April 7	...	1
April 8	...	2
April 9	...	2
April 10	1.60	
April 10	Curve B: epinephrin, 0.4 cc. subcutaneously	

The loss of weight was 38.5 per cent. Fifteen hours after the last curve the cat was in normal condition. The animal was killed with chloroform and an autopsy performed. No important changes





A, March 27, 1931, 0.4 cc., 1 to 1000 Adrenalin Subcutaneously, Amytal Anesthesia  
 B, April 10, 1931, 0.4 cc., 1 to 1000 Adrenalin Subcutaneously, Amytal Anesthesia  
 CHART VI.—Blood sugar curves after epinephrin injection in Cat 2 during thyroid feeding.



A, March 7, 1931, 0.4 cc., Adrenalin 1 to 1000 Intravenously Amytal Anesthesia  
 B, April 10, 1931, 0.4 cc., Adrenalin 1 to 1000 Intravenously Amytal Anesthesia  
 CHART VII.—Blood sugar curves after epinephrin injections in Cat 3 during thyroid feeding.

were found grossly or histologically. Chart VI is a graphic representation of the curves. Summary is given in Table 1.

Curves A and B (Chart VI) show distinct hyperglycemic responses. The thyroid extract that had been administered to the cat did not lessen the response; rather the Curve B after the animal had ingested a great amount of thyroid shows a more marked hyperglycemia.

CAT 3. The epinephrin was injected into the saphenous vein. Anesthesia was the same as in Cat 1; the time interval between the injection of the amytal and the taking of the first blood sample was approximately 1 hour and 15 minutes. The following table shows the weight of the cat and the doses of thyroid given.

Date.	Body weight, kilos.	Thyroid, gm.
Mar. 14, 1931	2.25	2
Mar. 16	2.10	3
Mar. 17	2.00	3
Mar. 18	2.07	3
Mar. 19	...	3
Mar. 20	...	3
Mar. 21	...	4
Mar. 23	...	3
Mar. 24	...	4
Mar. 25	1.95	4
Mar. 26	...	4
Mar. 27	Curve A: epinephrin, 0.4 cc. intravenously	
Mar. 28	...	5
Mar. 30	...	5
Mar. 31	...	4
April 1	...	3
April 2	1.7	3
April 3	...	3
April 4	..	3
April 6	...	3
April 7	1.5	1
April 8	...	2
April 9	..	2
April 10	Curve B: epinephrin, 0.4 cc. intravenously	

The cat lost 37.7 per cent of its body weight. It was found to be in normal condition about 15 hours after the last curve was completed. It was killed with chloroform and an autopsy performed. No important pathologic changes were found grossly or microscopically. The curves in Chart VII show an unquestionable hyperglycemic response to epinephrin. Although B is less of a reaction than A, it represents a distinct rise. Summary is given in Table 1.

Discussion. The findings of Burn and Marks,<sup>1</sup> and Marks<sup>11</sup> that prolonged thyroid feeding in rabbits resulted in a failure of epinephrin to cause a hyperglycemia and produced a fatal hypoglycemia was corroborated in 1 rabbit as a preliminary experiment. This animal showed no epinephrin hyperglycemia after feeding 2.55 gm. of desiccated thyroid; on the other hand, in the cats which

were approximately the same weight, 31, 82 and 70 gm. of desiccated thyroid fed over longer periods of time failed to prevent a hyperglycemia after epinephrin. In dogs the results were most striking: After 280 gm. and 647 gm. of desiccated thyroid over 50 and 37 days respectively epinephrin still produced a marked hyperglycemia. It is well known that dogs tolerate enormous amounts of thyroid as well as epinephrin, and it is possible that this normal resistance of the dog to thyroid is responsible for these results. The cats, however, seemed much more sensitive to thyroid feeding and yet showed no absence of the hyperglycemic response.

Amytal apparently had no effect in preventing hyperglycemia, as can be noted by comparing the curves done under amytal with those done without amytal.

Chemical determinations of liver glycogen in these animals were not made. It was not considered advisable to introduce such conflicting factors as biopsies of the liver in the course of thyroid feeding and epinephrin curves. If in any dog or cat a point had been reached where epinephrin failed to cause hyperglycemia glycogen determinations would have been made of necessity before concluding that thyroid feeding had depleted the liver of glycogen. But in the presence of an immediate hyperglycemic reaction to epinephrin, such as occurred in all the dogs and cats, the presence of glycogen stores seemed obvious, because, although muscle glycogen may be converted into lactic acid, and the latter synthesized into liver glycogen, the immediate rise in the blood sugar after epinephrin is generally conceded to be due to mobilization of liver glycogen.

The effect of epinephrin injections in leading indirectly to later deposition of glycogen in the liver must be considered as a factor opposing the loss of glycogen usually attributed to thyroid feeding. However, the epinephrin injections were separated by such long intervals that any effect of epinephrin injections in increasing liver glycogen would be more than offset by the effect of daily doses of thyroid if it is true that thyroid feeding depletes liver glycogen.

Although these experiments were primarily concerned with the blood sugar response to epinephrin during excessive thyroid feeding, certain deductions seem logical in respect to the effect of thyroid feeding on the storage of glycogen.

In other words, the question resolves down to whether or not the blood sugar response to epinephrin is an adequate test for liver glycogen. Although this belief has not been universally accepted, there is abundant evidence in favor of it. Markowitz<sup>10</sup> has shown that when the livers of rabbits have been entirely depleted of glycogen by starvation followed by strychnin shivering the injection of epinephrin does not cause a hyperglycemia; but if traces of glycogen remain there ensues a hyperglycemia of delayed onset,

the degree of which depends on the amount of glycogen present in the liver. According to Brill,<sup>2</sup> accelerated and augmented glycogenolysis produces the hyperglycemia following epinephrin, the extent of which is dependent to some extent on the quantity of glycogen in the liver. He further suggests that inasmuch as glycogen stores of skeletal and heart muscle are not demonstrably affected by epinephrin in the hepatectomized animal, they apparently are not so affected in animals with their livers intact. Olmsted and Coulthard<sup>12</sup> report from their experimental work that the blood sugar response to epinephrin depends to a considerable extent on the presence of sufficient amounts of glycogen in the liver.

Cori and Cori<sup>4</sup> showed that epinephrin promotes the decomposition of body glycogen with the production of lactic acid; this lactic acid is transported by the blood to the liver, and there is changed to glycogen. Thus the muscle glycogen is actually decreased while the liver glycogen is increased at 3 hours, but decreased at 15 minutes; but the glycogen store of the liver is the only direct source of blood sugar. The results of their work show how under the influence of epinephrin the muscle glycogen becomes an indirect source of blood sugar. But it is dependent on the presence of the liver and the escape of lactic acid from the muscles. The normal functioning of the liver in the carbohydrate balance must not be too greatly damaged, for the liver is necessary in this course of events. Apparently the Coris' views differ from those of others not in denying that the liver glycogen is the direct source of the increased blood sugar after epinephrin, but in considering that the rise in blood sugar is not entirely accounted for in this way but also results from decreased utilization of blood sugar.

Sahyun and Luck<sup>14</sup> have found in rabbits a depletion of liver glycogen after epinephrin during the first 2 hours and an increase after 3 hours.

In our experiments we were concerned almost primarily with the blood sugar response immediately following the injection of epinephrin. Eadie<sup>7</sup> has found from his work with cats under amytal anesthesia that the glycogen content of the muscles 1½ hours after the injection of epinephrin was unchanged, while that of the liver was reduced practically to zero. He suggests that the difference between his results and the earlier work of Cori and Cori might be explained by the difference of species. It seems, therefore, that the work of Cori and Cori does not appear as evidence which disproves that the hyperglycemic response to epinephrin is an indication of the presence of glycogen in the liver. Moreover, from the result of experiments on animals with livers removed it has been deduced that glycogen of the liver is the only direct source of blood sugar.

In our experiments it was necessary to use large doses of epinephrin and, since after the thyroid feeding the animal becomes extremely sensitive to epinephrin, there usually resulted marked

changes in respiration, and in dogs foamy fluid sometimes exuded from the mouth, and sometimes cyanosis occurred. The hyperglycemia, therefore, was probably partly an asphyxial hyperglycemia in the dogs, but even so, this indicated that there was a large reserve of glycogen. The rabbit under the same conditions of respiratory disturbances failed to show hyperglycemia in the late stage of thyroid feeding.

In discussions of the pharmacologic and physiologic effects of the administration of thyroid gland, it is generally stated that liver glycogen becomes depleted. To what extent this occurs, how constant a phenomenon this is, what degree of hyperthyroidism is necessary, or how long thyroid gland must be administered in order to bring about this condition is rarely quoted. Cramer and Krause<sup>5</sup> reported that they were able to deplete or reduce to a trace the glycogen from the livers of cats and rats fed on a carbohydrate-rich diet when small amounts of fresh thyroid were fed over a period of from 1 to 3 days. We have found this work quoted quite frequently (Cushny,<sup>6</sup> John,<sup>8</sup> Cameron<sup>3</sup> and Sanger and Hun<sup>15</sup>). Cameron<sup>3</sup> states: "Cramer and Krause have shown that the addition of thyroid to the diet of certain animals causes diminution and even complete exhaustion of the glycogen reserves of the body. According to Cramer, this is due to a direct action on the glycogenolytic function of the liver by the thyroid, which is opposed by the pancreatic hormone." Kuriyama<sup>9</sup> found that thyroid feeding rapidly reduced the glycogen in the livers of rats to a minimum, and reported also that glycogen storage does not occur readily in hyperthyroid rats, even though they are fed on a carbohydrate-rich diet. John<sup>8</sup> states that glycogen depletion occurs in hyperthyroidism, and suggests the following factors as influencing the disappearance of glycogen: "(a) Toxic influences which directly affect the parenchyma of the liver cells; (b) a high metabolic rate which causes increased consumption of carbohydrate and depletes the insulogenic stores, which in turn depletes the glycogen store in the liver."

Richardson, Levine and Du Bois,<sup>13</sup> estimating the glycogen storage in 2 patients with exophthalmic goiter, concluded that there was no impairment of glycogen storage.

Youmans and Warfield<sup>16</sup> found that the functional efficiency of the liver of dogs as tested by phenoltetrachlorophthalain was not affected by large doses of thyroid over short periods or smaller amounts of thyroid over longer periods of time, while in 50 per cent of thyrotoxic patients studied there was impaired liver function according to this test. They suggest that in human beings increased thyroid activity may cause the liver to be glycogen-free or glycogen-poor and this condition might make it more susceptible to injury by some toxic agent present in the disease.

The work of Cramer and Krause<sup>5</sup> would lead one to believe that it was a relatively easy matter to deplete the liver of glycogen in cats and rats by thyroid feeding. Their preparation was the fresh sheep thyroid. They report that the liver was either completely depleted of glycogen or that only traces remained after feeding usually about three or four lobes, more often less, over a period not exceeding 8 days. They reported that with a dose of three lobes three times in 1 day to a cat the glycogen was reduced to a trace.

Other authors seem to have taken their work as applicable to other animals and to human beings. That the liver glycogen is reduced in man is believed by many, although there is a certain amount of work that contradicts this view. Probably the degree of thyrotoxicosis determines this. There is abundant evidence which points to hepatic damage, as evidenced by abnormal glucose tolerance responses and other hepatic functional tests. Sanger and Hun,<sup>15</sup> studying patients with exophthalmic goiter, reported that the majority of patients showed abnormal blood sugar curves, but that some strikingly toxic cases showed normal curves. John<sup>8</sup> stated, after studying a number of patients with toxic goiter, that he was unable to demonstrate any glucose tolerance curve specific for hyperthyroidism. Since it is obviously strongly contraindicated to carry out an epinephrin curve in human hyperthyroidism, the method used in our animals is not applicable to man.

**Summary and Conclusions.** 1. Feeding 2.55 gm. of desiccated thyroid to 1 rabbit over a period of 21 days resulted in a progressive loss of body weight, decrease in the hyperglycemic response to epinephrin and, finally, an absence of hyperglycemic response, similar to the findings of Burn and Marks, and Marks, with a fatal hypoglycemic response to epinephrin when the liver glycogen was apparently depleted.

2. The feeding to 3 cats of 31, 82 and 70 gm. of desiccated thyroid, over a period of 15, 35 and 27 days respectively, resulted in loss of body weight, but no definite decrease in the hyperglycemic response to epinephrin.

3. The feeding to 2 dogs of 280 and 647 gm. of desiccated thyroid, over a period of 50 and 37 days respectively, resulted in no definite loss of body weight and no definite decrease in the hyperglycemic response to epinephrin.

4. It is probable, for the reasons outlined in the body of the paper, that the hyperglycemic response to epinephrin in dogs and cats indicated that the liver glycogen had not been depleted by thyroid feeding under the conditions of the experiment.

5. Though we hesitate to draw basic conclusions because of the limited number of experiments, the results at least show the great resistance of dogs and cats to thyroid. The reaction of these species is probably an exception. Since man is more sensitive than animals to thyroid, it would seem likely that the liver glycogen may decrease

in man more as it does in the rabbit than as in the resistant dog and cat, but it is obviously impossible to prove this in man.

NOTE.—These experiments were carried out under the direction of Dr. I. T. Zeckwer, to whom we extend our best thanks for her constant help both in the experimental work and in the preparation of the manuscript.

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### VARIATIONS IN THE PANCREATIC DUCTS AND THE MINOR DUODENAL PAPILLA.\*

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It is rather surprising to find, in reviewing the literature on the pancreas, that certain aspects of its anatomic structure have not as yet been sufficiently studied. Accordingly a special study was made of 25 autopsy specimens at the Philadelphia General Hospital with chief reference to the arrangements of the pancreatic ducts, their drainage, and the patency of the minor duodenal papilla. The practical significance of our findings will be discussed later.

According to the usual description given, the pancreas possesses two ducts: the larger and more constant is the pancreatic duct or duct of Wirsung; the smaller and less constant is the accessory pancreatic duct or duct of Santorini. To quote Baldwin, the duct of Wirsung, "beginning in the tail of the pancreas courses from left to right through the body and neck to the head of the gland, where

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it bends caudally, after receiving the accessory duct and, traversing the head of the gland, perforates the duodenal wall to empty into the duodenum in company with the common bile-duct, by way of the major papilla (which contains their common opening, the papilla of Vater) . . . The accessory duct is confined to the cephalo-ventral segment of the head which it traverses from its point of junction with the main duct to the minor duodenal papilla, where it either empties into the duodenum or terminates blindly. This minor papilla in the duodenal mucosa bears a cephalo-ventral relation to the major papilla and lies about 1.8 cm. from it."

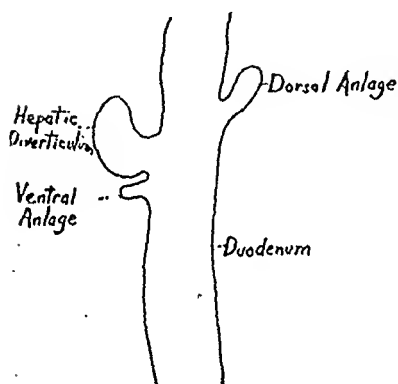
It was in 1641 that Moritz Hoffmann discovered the pancreatic duct within the pancreas of the turkey. A year later Wirsung dissected the duct in the pancreas of a human body, and observed that it was sometimes double. Judging from his reproduction of the duct he evidently believed that the vascular supply of the spleen came by way of the pancreas. "To Santorini belongs the credit for the first description of the accessory pancreatic duct, and for the first representation approximating accuracy of the arrangement of the ducts in the adult human pancreas." (Baldwin.) Interest gradually lagged, and it is only since the time of Claude Bernard, who in 1846 revived interest in the accessory duct, that much attention has been paid to the relations of it to the main duct and to the duodenum. In 1903, Opie investigated this problem in his monumental work on *Disease of the Pancreas*.

**Method.** The method used in the present study is similar in principle to that employed by Opie. The duct of Wirsung was exposed by transverse section of the body of the pancreas. A solution of methylene blue was injected at low pressure until it issued from an orifice in the duodenum. This opening was then compressed with a forceps, and the injection was continued at somewhat higher pressure to determine whether a second orifice was patent. The patent papillæ were next tied off at their openings into the duodenum, and the injection was continued in order to be certain that the small branches of the ducts would be distended. If fluid regurgitated through the common bile duct this also was tied off. The dissection of the ducts was facilitated by the presence of the methylene blue which stained the lining tissue very nicely. At the completion of the dissection the common bile duct was dissected to its point of entrance into the papilla of Vater, in order to verify which was the duct of Wirsung. The minor papilla was looked for only occasionally, as there is almost unanimous agreement among investigators concerning its position. The plan adopted was to call the largest branch the duct of Santorini. Of course, this might lead one astray, as size is no indication of embryologic development. But in practically every case the duct of Santorini was so large, compared to the other branches of the duct of Wirsung, that little doubt existed in our mind as to the correctness of our view. To quote Claude Bernard, the duct of Santorini "appears to be formed by the bifurcation of the larger duct, but, unlike the latter, diminishes in caliber as it approaches the intestine." The ideal method would be to trace the duct of Santorini to its termination in the minor papilla. Such a method usually requires serial sections. Moreover, in many cases this method would fail, inasmuch as the duct of Santorini normally atrophies completely in its terminal portion



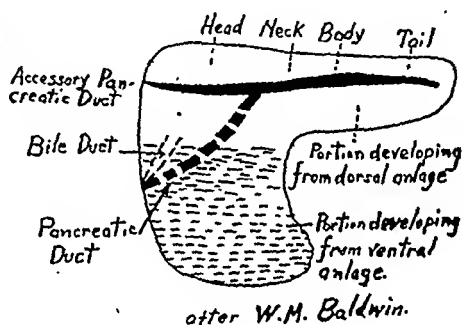
in a large percentage of specimens. Very little reference is to be found in the literature as to the criteria adopted by the various investigators in their choice of what to call the duct of Santorini.

**Development of the Pancreas.** As it is impossible to understand peculiarities of the ducts without a knowledge of the development of the pancreas, it may be well to review briefly this phase of the subject. Our knowledge dates, in effect, from 1888, when Phisalix was the first to explain embryologically the presence of two pancreatic ducts. The development of the pancreas is slightly preceded by that of the liver which "makes its appearance as a projection upon the ventral wall of what will subsequently become the duodenum" (Opie). The pancreas arises as an outgrowth from the intestinal tube during the early weeks of intrauterine life. There



after G. Cameron

Fig. 1a



after W.M. Baldwin.

Fig. 1b

FIG. 1.—Embryology of the pancreas. A shows relationship of dorsal and ventral anlagen to the hepatic diverticulum. B shows the portions of the pancreas that develop from the dorsal anlage and ventral anlage as well as the mode of formation of the pancreatic duct and accessory pancreatic duct.

are two anlagen, or outgrowths from the intestine; dorsal and ventral. The ventral anlage is smaller and is situated in the inferior angle between the hepatic diverticulum and the intestine. According to some writers (Debeyre and Helly, among others) two ventral anlagen (a right and a left) are occasionally found. The dorsal anlage is much larger than the ventral anlage, and arises from the intestine between the hepatic diverticulum and the stomach. It rapidly elongates into a duct. The ventral and dorsal anlage give rise to separate pancreatic tissue masses. (Fig. 1A.)

Fusion of the two masses occurs as a result of two factors:

1. Rotation of the intestinal tube so that the ventral and dorsal anlage become medial and lateral respectively.

2. Active growth of the ventral toward the dorsal process. "The bile duct develops from the most proximal portion of the hepatic anlage, grows dorsally from its position on the right side of the intestine, and the ventral process (accompanying it) is brought into close relation with the dorsal process and by the third month has anastomosed with it" (Cameron). Presumably the ventral anlage gives rise to the caudal portion of the head of the pancreas, and most of the uncinata process (which is the angle of junction of the lower and left lateral borders). The dorsal anlage gives rise to the remainder of the pancreas, namely, tail, body, neck and part of the head.

At an early period an anastomosis develops between the duct of the ventral anlage and that of the dorsal anlage. After this occurs, "that part of the upper or originally dorsal duct which lies between the duodenal orifice and its anastomosis with the lower duct undergoes partial atrophy, and the lower channel increasing in size appears to be a continuation of the large duct" (Opie). (Fig. 1B.)

In other words, the duct of Wirsung in the adult is represented by a continuous channel formed by the distal portion of the duct of the dorsal process, the anastomosis, and the duct of the ventral process. The duct of Santorini is represented by the proximal portion of the duct of the dorsal process. J. F. Meckel's statement that atrophy of the duodenal end of the duct of Santorini is the developmental rule is of the greatest significance in explanation of the causative factors involved in the production of the numerous anomalies observed.

In 1914 Corner, studying the development of the ductal system in the pancreas of the pig, found that it develops a primitive plexus strikingly similar to that of the primitive blood plexus, and there is some evidence that the same physical laws hold true for the ductal system. It is quite probable, as a result of his investigations, that a flow of secretion occurs through the plexus before the main duct makes its appearance. These observations offer a new basis for an explanation of the origin of variations of the pancreatic ducts—as will be shown later.

*Position of Main Pancreatic Duct.* The main pancreatic duct is quite variable in its position within the pancreas. Cameron in 1924 reported 80 per cent near the posterior surface and 20 per cent near the anterior surface or center. We found the reverse to be true. (Table 1.)

TABLE 1.—POSITION OF MAIN PANCREATIC DUCT.

	This series.		Cameron.	
	No. of cases.	Per cent.	Per cent.	No. of cases.
Posterior . . . . .	6	24	80	80
Center . . . . .	9	76	20	20
Anterior . . . . .	10			

We were able to verify Baldwin's statement that "at the head of the gland, the main duct inclines somewhat abruptly caudally and dorsally with the convexity toward the right and approaches the dorsal surface of the head of the gland. Reaching the level of the major duodenal papilla, the duct now runs almost horizontally to the right to join with the caudal aspect of the common bile duct, and empty with it into the major papilla." This statement is true in a majority of the cases, but there is a large group of cases (chiefly those in which the pancreatic duct is situated near the center) in which the duct is practically a straight tube with the major papilla midway between the cephalic and caudal borders, and between the anterior and posterior borders of the head of the pancreas. It was noted that the bile duct invariably lies dorsal to the head of the pancreas and runs caudally toward the median surface of the second portion of the duodenum to end in the papilla of Vater.

*Relative Sizes of Duct of Santorini and Duct of Wirsung.* Three specimens (12 per cent) showed the duct of Santorini to be equal to or larger than the duct of Wirsung. Opie and Charpy each reported 10 per cent; whereas Schirmer reported 3 per cent and Baldwin 4 per cent. (Table 2.)

TABLE 2.—RELATIVE SIZES OF DUCT OF SANTORINI AND DUCT OF WIRSUNG.

	No. of cases.	Inversion.	Per cent inversion.
Schirmer . . . . .	104	3	3
Charpy . . . . .	30	3	10
Bernard . . . . .	..	1	
Morel and Duval . . . . .	?	1	
Opie . . . . .	100	11	11
Bimar . . . . .	?	1	
Baldwin . . . . .	76	3	4
Cameron . . . . .	100	10	10
Morse . . . . .	?	1	
Author . . . . .	25	3	12

Most investigators have found that in 10 per cent of cases the duct of Santorini is as large as, or larger than, the duct of Wirsung.

*Presence of Accessory Duct.* The accessory duct was present in every case, as has been reported almost universally. In fact, cases of so-called absence of the accessory duct are now looked upon with suspicion. (Table 3.)

TABLE 3.—PRESENCE OF ACCESSORY DUCT.

	Present.	Absent.
Schirmer . . . . .	101	3
Charpy . . . . .	29	1
Helly . . . . .	50	0
Verneuil . . . . .	20	0
Hamburger . . . . .	50	0
Sappey . . . . .	11	0
Opie . . . . .	100	0
Baldwin . . . . .	76	0
Cameron . . . . .	100	0
Author . . . . .	25	0

**Patency of the Minor Papilla.** The minor papilla is situated at a variable distance above the major papilla. It is often very small and inconspicuous, but it is probably always present, as the work of Opie, of Baldwin and of Cameron bear out. A great deal of difficulty is encountered in determining the percentage of cases in which the duodenal papilla is patent. As Opie states, "on the one hand, a small quantity of mucus within the minute lumen may readily prevent the penetration of injected material, and on the other hand, Henle states, material injected under considerable pressure may produce a false passage." Various methods have been used to settle this question. Schirmer used an insufflation method, Opie injected Berlin blue under pressure, Claude Bernard injected metallic mercury, etc. A second group of investigators used a microscopic method, by which serial sections were made through the papilla. As might be expected, discrepancies in results are quite marked—a good deal depending on the method used. Thus, Opie found a considerable number of specimens (48 per cent) in which it was not possible to force, from the lesser papilla, fluid injected under low pressure into the duct of Wirsung. In such instances he made serial sections through the minor papilla, and in 21 of 100 cases the lumen was not found demonstrably continuous with that of the intestine. In our series we found only 3 of 25 cases to have a patent lumen. Probably the incidence would have been much increased had a microscopic method been used as a check. Insofar as clinical significance is concerned, our results confirm those of Opie—10 per cent of cases show the minor papilla to be sufficiently patent to act as safety valves should bile be dammed up in the duct of Wirsung.

TABLE 4.—CONDITION OF DUCT OF SANTORINI AT MINOR PAPILLA.

Author.	Patent.	Closed.
<i>Microscopic Method.</i>		
Helly . . . . .	40	10
Baldwin . . . . .	45	5
<i>Injection Method (a Microscopic Method in Some Cases).</i>		
Schirmer . . . . .	85	19
Charpy . . . . .	9	21
Opie . . . . .	79	21
Verneuil . . . . .	20	0
Sappey . . . . .	16	1
Cameron . . . . .	77	23
Author . . . . .	3	22

*Drainage and Variations in Arrangement of the Ducts.* At first sight, the types and arrangements of the pancreatic ducts and their drainage seemed to present a chaotic condition, but when the results obtained by study of the 25 specimens are charted, certain relations become at once apparent. (Table 5.) The types encountered fall logically into 3 groups:

TABLE 5.—DISTRIBUTION OF DUCT OF SANTORINI (HEAD OF PANCREAS).

Specimen.	Position of duct of Wirsung within pancreas.	Patency of minor papilla.	Size of duct of Santorini compared with that of duct of Wirsung.	Ventrecephalic.		Dorsocephalic.		Ventrecaudal.		Dorsocaudal.	
				Mesial ‡.	Lateral ‡.	Mesial ‡.	Lateral ‡.	Mesial ‡.	Lateral ‡.	Mesial ‡.	Lateral ‡.
1	Posterior	Nonpatent	Smaller	✓	✓	✓	✓	✓	✓	✓	✓
2	Posterior	Patent	Smaller	✓	✓	...	...	✓	✓	✓	✓
3	Anterior	Nonpatent	Smaller	...	...	...	...	✓	✓	✓	✓
4	Anterior	Nonpatent	Smaller	...	...	...	...	✓	✓	✓	✓
5	Middle	Nonpatent	Smaller	...	...	...	...	✓	✓	✓	✓
6	Middle	Nonpatent	Smaller	...	...	...	...	✓	✓	✓	✓
7	Anterior through tail, body, head (D.S.); Posterior through head (D.W.)	Patent	Larger	✓	✓	✓	✓	✓	✓	✓	✓
8	Anterior (D.S.)	Patent	Larger	✓	✓	...	...	✓	✓	✓	✓
9	Posterior (D.W.)	Nonpatent	Equal	✓	✓	✓	✓	✓	✓	✓	✓
10	Anterior	Nonpatent	Smaller	✓	✓	✓	✓	✓	✓	✓	✓
11	Anterior	Nonpatent	Smaller	✓	✓	✓	✓	✓	✓	✓	✓
12	Middle	Nonpatent	Smaller	✓	✓	✓	✓	✓	✓	✓	✓
13	Middle	Nonpatent	Smaller	✓	✓	✓	✓	✓	✓	✓	✓
14	Middle	Nonpatent	Smaller	...	...	...	...	✓	✓	✓	✓
15	Middle	Nonpatent	Smaller	✓	✓	✓	✓	✓	✓	✓	✓
16	Anterior	Nonpatent	Smaller	✓	✓	✓	✓	✓	✓	✓	✓
17	Anterior	Nonpatent	Smaller	✓	✓	✓	✓	✓	✓	✓	✓
18	Middle	Nonpatent	Smaller	...	...	✓	✓	✓	✓	✓	✓
19	Middle	Nonpatent	Smaller	✓	✓	✓	✓	✓	✓	✓	✓
20	Posterior	Nonpatent	Smaller	✓	✓	✓	✓	✓	✓	✓	✓
21	Middle	Nonpatent	Smaller	...	...	✓	✓	✓	✓	✓	✓
22	Posterior	Nonpatent	Smaller	✓	✓	✓	✓	✓	✓	✓	✓
23	Posterior	Nonpatent	Smaller	✓	✓	✓	✓	✓	✓	✓	✓
24	Posterior	Nonpatent	Smaller	✓	✓	✓	✓	✓	✓	✓	✓
25	Anterior	Nonpatent	Smaller	✓	✓	✓	✓	✓	✓	✓	✓

Table 5 shows: (1) Position of duct of Wirsung within pancreas. (See also Fig. 1.) (2) Patency of minor papilla—the minor papilla is patent structurally, and probably functionally, in 3 specimens. (3) Size of duct of Santorini compared with that of duct of Wirsung. In 3 specimens the duct of Santorini is equal to, or larger than, the duct of Wirsung. (4) Distribution of duct of Santorini. The head of the pancreas is divided into eight portions and the drainage of the duct of Santorini in the various specimens is indicated.

GROUP A. In which the duct of Santorini is present only in the cephalic portion of the head of the pancreas. Specimens, I, II, X, XV, XVI, XVII, XXIV, XXV—total of 8. (Fig. 2.)

GROUP B. In which the duct of Santorini is present only in the caudal portion of the head of the pancreas. Specimens, III, IV, V, VI, XIII, XX, XXI, XXIII—total of 8. (Fig. 2.)

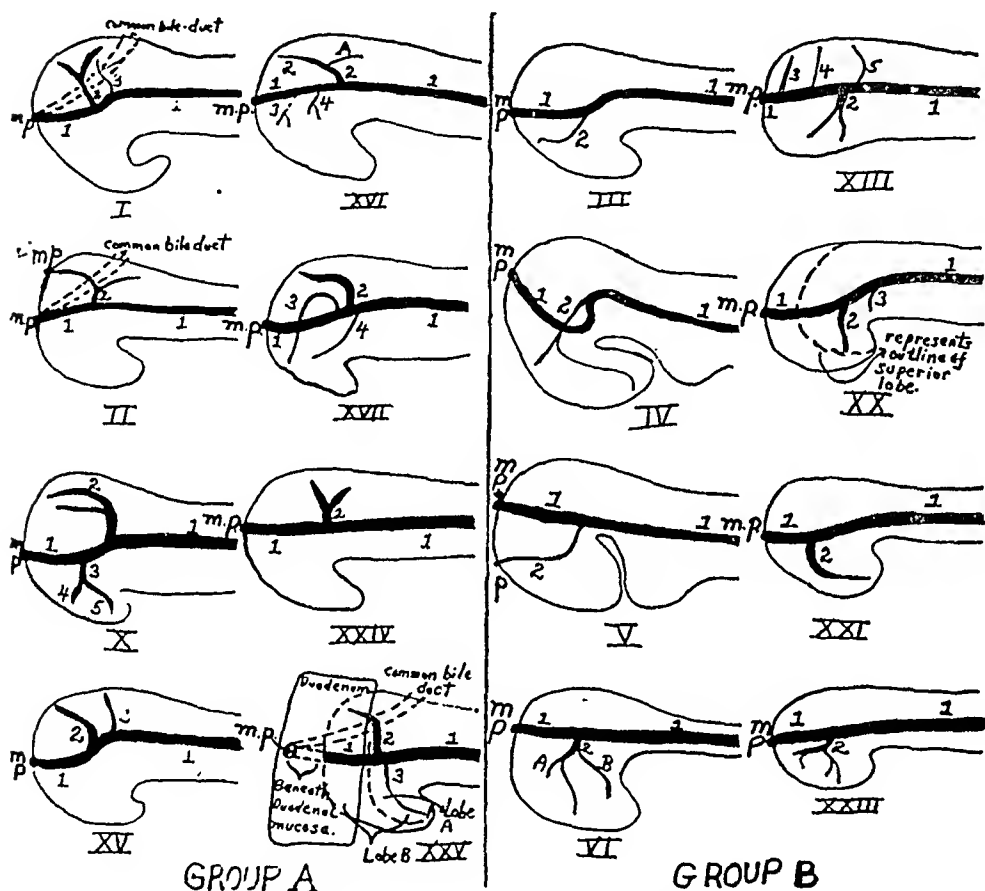


FIG. 2.—Position of duct of Santorini. Group A: Specimens in which the duct of Santorini is present only in the cephalic portion of the head of the pancreas. Specimens I and II show common bile duct, which has similar position in all of the specimens. Specimen XXV shows the major papilla entirely separated from the pancreas itself. It also shows the interlobar fissure, which separates lobe A (the lobe of Santorini) and lobe B (the lobe of Wirsung). Group B: Specimens in which the duct of Santorini is present only in the caudal portion of the head of the pancreas. Specimen V shows the duct of Santorini ending in a closed bulb beneath the minor papilla. *m.p.*, major papilla; *m.p.*, patent minor papilla; 1, duct of Wirsung; 2, duct of Santorini; A, B, C, branches of duct of Santorini; 3, 4, 5, branches of duct of Wirsung.

GROUP C. In which the duct of Santorini and its branches are present in both caudal and cephalic portions of the head of the pancreas—total of 7. (Fig. 3.)

I. Duct of Santorini chiefly in cephalic portion; IX, XI, XII, XIX—total of 4.

II. Duct of Santorini chiefly in caudal portion; XVIII, XXII—total of 2.

III. Duct of Santorini equally in cephalic and caudal portions; 14—total of 1.

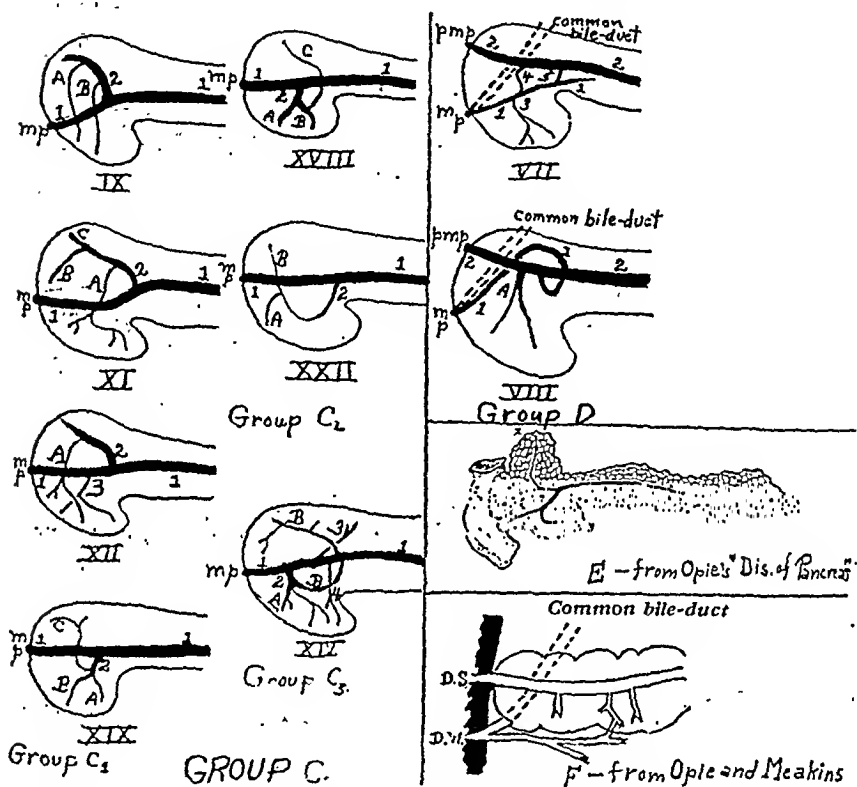


FIG. 3.—Group C: Specimens in which duct of Santorini is present in both caudal and cephalic portions of head of pancreas. Group C<sub>1</sub>: Duct of Santorini chiefly in cephalic portion. Group C<sub>2</sub>: Duct of Santorini chiefly in caudal portion. Group C<sub>3</sub>: Duct of Santorini equally in cephalic portions. Group D: Shows distinct anomalies. Specimen VII shows the embryonic arrangement of the ducts very well. (Note the close resemblance to the specimen of Opie and Meakins shown in F.) In both Specimens VII and VIII the minor papilla is structurally, as well as functionally, patent. Group E: From Opie's *Disease of the Pancreas*. Pancreas showing the two lobes which form the head. The lower part (x) of the lobe, corresponding to the duct of Santorini, is drawn upward to expose the lobe (y) corresponding to the duct of Wirsung. Group F: Diagram showing the relative sizes of the two pancreatic ducts in a case of acute hemorrhagic pancreatitis reported by Opie and Meakins. mp, major papilla; pmp, patent minor papilla; 1, duct of Wirsung; 2, duct of Santorini; A, B, C, branches of duct of Santorini; 3, 4, 5, branches of duct of Wirsung.

GROUP D. A fourth group, D, may be added in which are placed distinct anomalies; VII, VIII—total of 2. (Fig. 3.)

In Fig. 4 are shown some of the ductal arrangements found by Opie. It will be noted that in practically every case the duct of

Santorini receives a branch from the caudal portion of the head of the pancreas. In Specimens IV and VII the embryonic arrangement has persisted and the duct of Santorini has remained the chief duct of the gland. In Specimen V atrophy has occurred at the proximal, instead of the terminal, portion of the duct of Santorini. Evidently the duct of Santorini in this instance supplies an isolated portion of the head of the pancreas in close proximity to the minor papilla.

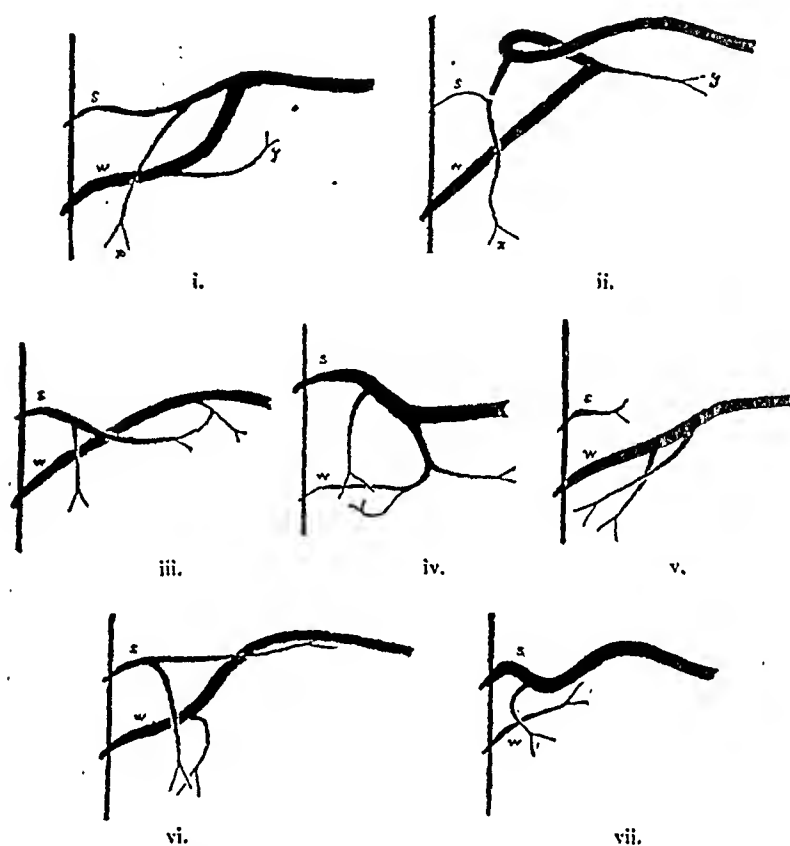


FIG. 4.—Varying relations of the duct of Santorini (s) to the duct of Wirsung (w). Drawn from dissected specimens. (From Opie's *Disease of the Pancreas*.) In almost every case the duct of Santorini receives a branch from the caudal portion of the head of the pancreas. In Specimens IV and VII the embryonic arrangement has persisted, and the duct of Santorini has remained the chief duct. In Specimen V atrophy has occurred at the proximal, instead of the terminal, portion of the duct of Santorini.

It is surprising to find that so little detailed attention has been paid to the question of drainage. Only 3 statements on this subject have been found—by Opie, Charpy and Baldwin. Opie found the duct of Santorini to drain the anterior and lower part of the head. According to Charpy the accessory duct drains the superior lobe of the gland. Baldwin found the duct of Santorini to drain the ventrocephalic portion in the immediate neighborhood of the minor papilla, and a small portion of the ventrocaudal segment. It is



quite evident, therefore, that no very close agreement exists concerning the drainage of the duct of Santorini.

In Group A the distribution of the duct of Santorini is quite variable. It may drain the dorsocephalic or ventrocephalic portions, or both. Which it does in a given case would seem to depend on three factors:

1. The relative rapidity of growth of the two anlagen.
2. Their direction of greatest growth as well as their relative position, one to the other.
3. The degree of atrophy which the duct of Santorini undergoes following the formation of the duct of Wirsung. It seems to us that there must inevitably occur numerous combinations of the above factors, and such an explanation may easily account for the very numerous anomalies that are so commonly observed. For example, in Group B the situation is entirely the reverse of that in Group A. Here we find the distribution to be the contrary of what has been reported in the literature. We may assume that in this group the atrophy of the duct of Santorini in the cephalic portion has been complete, or that the relative rate of growth of the ventral anlage was extremely rapid, and directed sharply cephalad. In Group B, by far the greatest number of specimens show the duct of Santorini to supply the entire caudal portion of the head of the pancreas.

Group C probably represents the "typical" arrangement of the duct of Santorini. In this group seem to fit most of the specimens of Opie, already mentioned. The same forces operate in Group C as in Groups A and B. The above factors may afford an adequate explanation of the *drainage*, but in considering the *form* of the ducts, it seems to us that the work of Corner (previously mentioned) on duct plexuses offers an interesting explanation. The old view held that the irregularities in the course of the ducts were due to abnormal development or growth of one or both anlagen. This view falls when it is observed, as Corner showed, that "before the chief duct is formed the two anlagen are completely fused, so that the anlagen play no great part in the production of variations in the course of the ducts, except insofar as they limit the plexus to one, or at most two, points of outlet into the duodenum. On the other hand, the primitive plexus explains all the variations, and the abnormalities are undoubtedly produced in a way exactly like those of the blood-vascular system, as demonstrated by Evans. Just as a blood-capillary supply the embryonic arm-bud or kidney may, for some reason, persist after its time and form an accessory brachial artery or renal vein, so at the time of appearance of the pancreatic duct, varying physical forces may lead the new channel through one or another mesh of the plexus . . . and in this way any imaginable variation may be produced, even loops and spirals, while the external form of the pancreas remains without change."

From what has been said concerning the embryology of the pancreas it will be remembered that the head of the pancreas is formed by the fusion of the dorsal and ventral anlagen. By dissection it is found that the degree of fusion is very variable. There is often found an interlobar fissure by which the head of the pancreas (chiefly the caudal portion) is divided into two distinct lobes corresponding to the two ducts. These lobes may be termed the lobe of Wirsung and the lobe of Santorini (Fig. 3*E*). Our results agree fairly closely with those of Opie, who found that "the lobe of Santorini (*x*), drawn upward in the figure, is larger than the lobe of Wirsung (*y*) which lies behind it, and being much wider from above down, forms the lower or descending part of the head. The lobe of Wirsung is a relatively narrow compressed mass of parenchyma, flattened antero-posteriorly and surrounding on all sides the duct of Wirsung."

The specimens in Group D (Fig. 3) are extremely interesting. Specimens VII and VIII illustrate the embryonic arrangement splendidly. The close resemblance of Specimen VII to the specimen described by Opie and Meakins (Fig. 3*F*) is readily apparent. Specimen V shows a minor papilla *below* the major papilla. Such a situation is contrary to what is reported in the literature. Specimen XXV is a remarkable one. It shows the major papilla opening into the duodenum entirely separate from the pancreas. Both the common bile duct and the duct of Wirsung pass transversely across the duodenum beneath the mucosa for a distance of about 1 inch before terminating in the papilla of Vater.

*Clinical Applications.* As may readily be inferred, the anatomic relationships of the duct of Wirsung and the duct of Santorini to each other and to the common bile duct are of great clinical importance. The classical work of Opie has shown how a small gall stone lodged at the orifice of the ampulla of Vater may divert bile into the pancreatic duct and produce hemorrhagic pancreatitis. In only 30 per cent of individuals are the anatomic conditions such that a small stone might divert the bile into the pancreatic duct. Moreover, we have confirmed Opie's finding that in 10 per cent of individuals the duct of Santorini is as large as, or larger, than the duct of Wirsung, and is patent at the site of the lesser papilla. Consequently 10 per cent of people are provided with safety valves, so to speak—even if other conditions are favorable for the incidence of acute hemorrhagic pancreatitis. For example, in Specimen VII (Fig. 3), even if a stone at the ampulla of Vater were capable of diverting bile into the duct of Wirsung, the bile could easily find its way into the duodenum through the large patent minor papilla, and acute hemorrhagic pancreatitis would not develop. Such facts explain, in part at least, the rarity of acute hemorrhagic pancreatitis as compared with the relative frequency of gall stone disease. On the other hand, the presence of such an anomalous arrangement in

10 per cent of people renders such individuals susceptible to acute hemorrhagic pancreatitis brought about by the entrance of irritant duodenal contents, by way of the anomalous duct of Santorini. The power of such material to cause the disease has been amply proved by experiment. As Opie states, "It is well known that increased pressure within the duodenum does *not* force duodenal contents into the bile duct or pancreatic duct after death." This is due to the presence of the sphincter of Oddi. Such a mechanism seems to be absent in the orifice of the anomalous duct of Santorini and intestinal contents may, under certain conditions, enter such a duct when the pressure within the duodenum is increased, as for example, by vomiting.

The anomalous arrangement mentioned above may also play an important rôle in the prevention of chronic interlobular pancreatitis. It is well known that this disease may be produced by ligation of the duct of Wirsung. Complete or partial occlusion of the duct of Wirsung in human beings may be caused by pancreatic calculi in the duct of Wirsung, by biliary calculi in the adjacent terminal portion of the common bile duct, or by neoplasms compressing or invading the gland. In 10 per cent of individuals, chronic interlobular pancreatitis is not very likely to occur, since the large patent duct of Santorini offers an adequate factor of safety.

Certain cases of acute hemorrhagic pancreatitis reported in the literature can be explained only on the basis of a knowledge of the common anomalies. Opie and Meakins reported a case in which the lesion was rather sharply confined to that portion of the pancreas supplied by the duct of Santorini. Investigation showed an anomalous duct of Santorini as the chief outlet of the gland. (Fig. 3*F*.) Similar cases have been reported by Johnstone and by Bassett, among others. Other puzzling cases probably have a similar etiology. A few months ago a patient was admitted to the Hospital of the University of Pennsylvania with complaint of sudden sharp epigastric pain, together with nausea and vomiting and a tentative diagnosis of mesenteric thrombosis (F. R., Index No. 20449, Surg. Serv.). At autopsy the primary lesion was found to be a subacute hemorrhagic pancreatitis sharply limited to the cephalic half of the head of the pancreas. In this case the degree of necrosis present prevented the duct of Santorini from being traced, but we seem justified in assuming the presence of an anomalous duct of Santorini as previously described. It is quite possible that many other puzzling surgical conditions of the abdomen, similar to the above, have heretofore been misdiagnosed simply because the possibility of an anomalous duct of Santorini has not been borne in mind.

**Summary.** A detailed description of the relationships of the duct of Santorini to the duct of Wirsung is given. A classification is offered of the various arrangements found, as well as a theory to account for such variations. The extraordinary variability of the pancreas in respect to size, shape and ductal arrangement is pointed

out. We have confirmed Opie's finding that in 10 per cent of individuals the duct of Santorini is functionally as well as structurally the chief outlet of the external pancreatic secretion, and that such anomalous arrangement may play an important rôle in the prevention or institution of acute hemorrhagic pancreatitis; that it is of great importance likewise in the etiology of chronic interlobular pancreatitis; and that this condition may account for certain puzzling cases of unexplained deaths.

NOTE.—I wish to express my appreciation to Dr. Krumbhaar for his kindly criticism and advice, as well as to Dr. McCutcheon and to Mr. Taggart, of the Philadelphia General Hospital, for their helpful coöperation.

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## THE PATHOGENESIS OF ACUTE SUPPURATIVE PAROTITIS.

### AN EXPERIMENTAL STUDY.\*

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ACUTE suppurative parotitis is a condition commonly encountered in the course of medical and surgical practice. So frequently is its occurrence an ill omen in prognosis that a clear knowledge of

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its pathogenesis is important. The condition appears most often as a complication following surgical operations and during the course of infectious diseases and debilitating states. Only occasionally does it develop primarily in an otherwise healthy individual. The mortality rate is usually high, being estimated at 30 per cent by Wagner,<sup>1</sup> at 42.8 per cent by Blair and Padgett.<sup>2</sup>

The literature holds many accounts of acute suppurative parotitis that consider the condition from clinical, pathologic and bacteriologic viewpoints. For an extensive survey of the question reference is made to the article by Custer,<sup>3</sup> (page 649 of this issue of this *Journal*). All of the authors have expressed their individual opinions concerning the common mode of infection of the gland. Not one has denied that many of the cases are due to an ascent of the infecting organism from the oral cavity to the parotid gland through Stensen's ducts, with a consequent secondary invasion of the glandular tissue. Some observers, however, believe that the gland becomes infected by way of the blood stream far more frequently than had been suspected previously. These authors base their opinions chiefly on the facts that the complication arises more frequently when operation has been carried out in a septic field and that very often the inflammation does not become evident until several days have passed after the operation.

Certainly the anatomic and bacteriologic findings support the theory of ductogenous infection. Anatomic studies indicate that early cases show involvement of the larger ducts; that later cases show extension through the small radicals secondarily involving periductal gland tissue and finally producing multiple abscesses centering upon the ducts.

In bacteriologic studies it has been shown that only rarely has the organism recovered from the parotid gland corresponded to that of a local focus elsewhere or to that of an existing general infection. Typhoid fever is the exception to this rule. The typhoid bacillus has been isolated from the parotid gland in cases of typhoid fever. *Bacillus typhosus*, however, can be cultivated from many organs during the acute stage of the disease, and when found in the parotid has been usually but one element of a mixed infection. The organisms most frequently isolated from cases of acute parotitis are those that normally exist in an avirulent state in the mouth and in the lower segment of Stensen's duct. Of these the *Staphylococcus aureus* is the chief offender.

Clinically there exist a number of factors that favor ascent of infection through the duct. The lowering of general resistance by infection and debilitation increases the relative virulence of the normal bacterial flora of the mucous surfaces. Diminution of the salivary flow during febrile states, general dehydration from vomiting, reflex diminution of salivary secretion in surgical procedures from anesthesia and visceral manipulation, as well as actual trauma

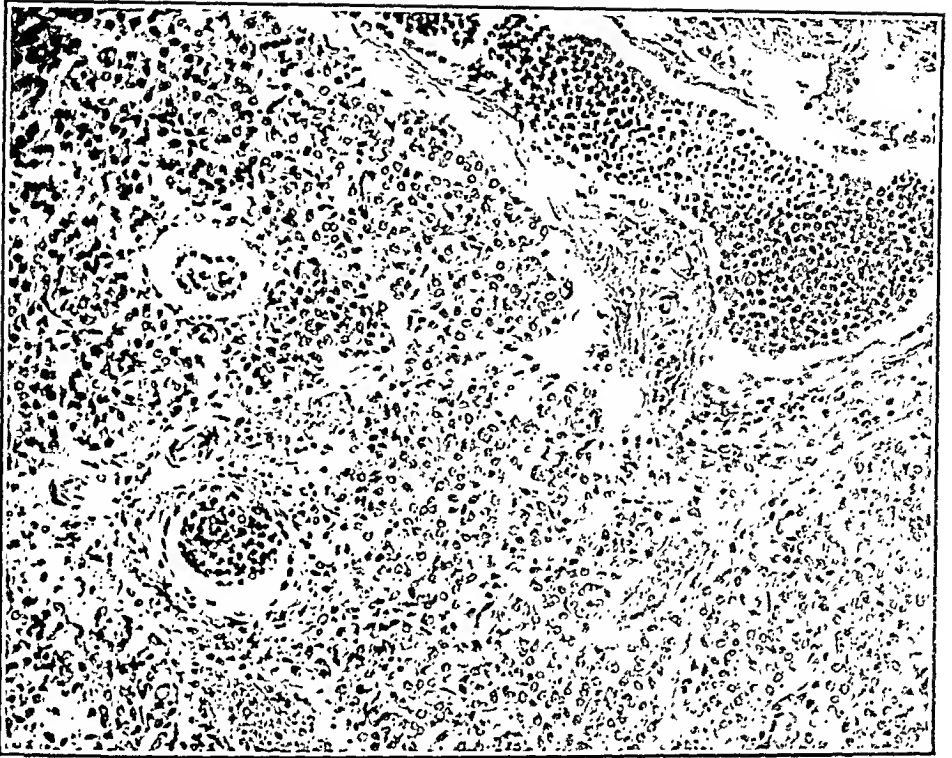


FIG. 1.—Ductogenous parotitis. (Dog 1098.) Note progressively decreasing involvement of the ducts as the smaller radicals are approached.



FIG. 2.—Hematogenous parotitis. (Dog. 1099.) (Same organism used in Dog 1098, Fig. 1.) Periductal gland tissue shows necrosis and round-cell infiltration. Smallest ducts most affected, largest least.

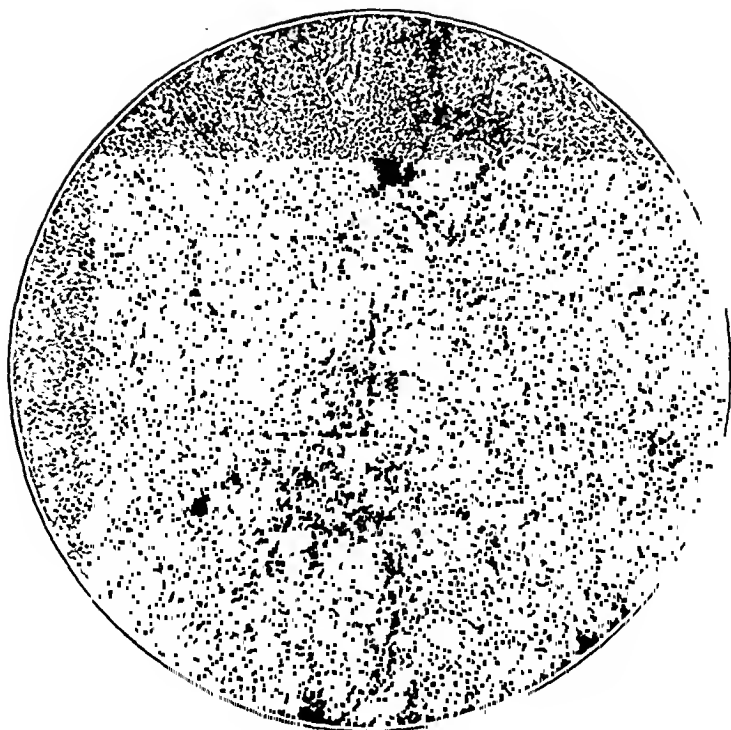


FIG. 3.—Hematogenous parotitis. (Dog. 7.) Note cellular exudate in gland tissue with little involvement of ducts.

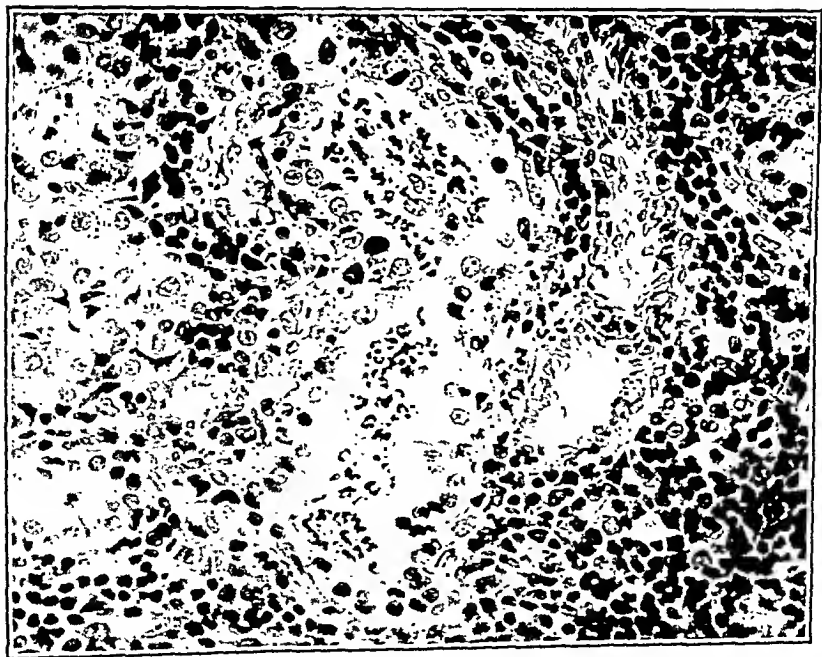


FIG. 4.—High power of outlined field in Fig. 3. The periductal exudate is round-cell. The intraductal exudate is neutrophilic. Lining epithelium intact; vascular endothelium hyperplastic.

to the gland by unskilled anesthetists, are among the more important factors causing lowered resistance.

Until 1914 the studies on acute suppurative parotitis had been based solely on clinical observations, bacteriologic findings and pathologic anatomy. Little experimental work had been done on the subject. Claissé and Dupré<sup>4</sup> had attempted to produce the condition in dogs by injecting organisms into the ducts, but they failed to produce suppuration except when they ligated the ducts or introduced foreign bodies into the lumens of the ducts.

In 1914 Rost<sup>5</sup> published an account of his experimental study of the question. He stated that he had been able to infect the parotid glands of dogs by injecting the same organisms into the ducts and the artery that supplies the gland with equal facility. He stated, furthermore, that *in both cases the pathologic picture was identical*.

Rost's report has been widely recognized and accepted; the descriptions and illustrations in his paper are convincing. A search of the literature fails to show any subsequent work of the same type that might be accepted as confirmation of Rost's work. For this reason it was decided to repeat his experiments and to observe the inflammatory response of the parotid gland to ductogenous and to blood-borne infections.

**Methods.**—In preparation for the actual experimental procedures, a careful examination was made of the anatomical relations of the parotid glands. The parotids are the largest oral glands; they are located, in the dog, in the superficial fascia on each side of the head just below the ear; they are organic, branched glands, subdivided into lobes and lobules; they drain into the oral cavity through Stensen's ducts which emerge opposite the second molar teeth of the upper jaws. These ducts are characterized histologically by a thick membrana propria and are lined by a two-layered columnar epithelial coat. As the duct branches repeatedly, the epithelium becomes simple columnar in type, passing through a transition stage of pseudostratified epithelium. The smallest ducts are lined with flat cells that are continuous with the large cuboidal cells of the alveoli.

The blood supply is furnished by twigs from the superficial temporal artery, a branch of the external carotid. The branches of these twigs generally follow the ducts through the connective tissue septa into the lobules, where they produce an abundant capillary network close to the basement membrane of the alveoli. The veins derived from these capillaries soon enter the interlobular tissue and accompany the arteries.

An injection of colored gelatin was made into the common carotid artery of a dog. The head was fixed in formalin and the arterial tree was dissected out. The exact blood supply of the parotid gland was determined and orientation obtained so that the superficial temporal artery could be picked up readily in a small operative field.

In the choice of bacteria to be injected we followed Rost's example in selecting hemolytic *Staphylococcus aureus*. Twenty-four hour bouillon cultures were used; in one group an autopsy culture of high virulence was injected,\* in another a culture of low virulence from a case of furunculosis

\* The culture of high virulence produced death in a rabbit within 24 hours following intravenous injection of 1 cc. of a 24-hour growth.



was used.\* In 2 cases we employed a mixed culture of staphylococci and pneumococci that was recovered from a human case of acute suppurative parotitis.

Our first series of experimental animals was composed of 13 adult dogs. Four dogs were selected for injection of bacteria into Stensen's duct. Nine received injections of bacteria into the superficial temporal artery. Two of this latter group were subjected to dehydrating measures, *i. e.*, purging and dry diet, for 24 hours prior to the operation.

The technique of the duct injections was as follows: The animal was anesthetized with sodium amytal. A blunted hypodermic needle was passed into the orifice of Stensen's duct. A syringe containing 2 cc. of 24-hour broth culture of hemolytic *Staphylococcus aureus* was fitted to the needle and the contents injected into the duct. Bilateral injections were made in all 4 dogs. In 3 of these dogs the duct on one side was ligated, the other not; in one both ducts were ligated. When the duct was to be ligated, a suture-ligature was passed about the needle in a half-hitch, the injection made, and the knot drawn tight as the needle was withdrawn.

For the injection of the arteries the following technique was used, with aseptic surgical methods: Under amytal anesthesia a 2-inch incision was made between the internal border of the sternocleidomastoid muscle and the trachea. By blunt dissection the external carotid artery was exposed and traced to the superficial temporal branch. This latter artery was carefully stripped of its surrounding fascia. An aneurysm needle was passed under the vessel so that the flow of blood through the artery could be temporarily stopped by a lift on the aneurysm needle. With the flow thus occluded the injection of 2 cc. of bacterial suspension was made by means of a hypodermic syringe fitted to a needle of small bore. The needle was withdrawn and the wound was packed tightly until oozing from the point of puncture had ceased. The operative field was antiseptitized by puddling with hexylresorcinol or mercurochrome. The wound was closed in layers with interrupted silk sutures.

After recovery from anesthesia the dogs were returned to the animal house and observed daily until they died or were chloroformed. The period of postoperative life varied from 12 hours to 14 days. Autopsies were performed promptly after death; the parotid glands were removed and inspected for gross manifestations of inflammation and suppuration. Sections were made of large areas of the glands for histologic study.

**First Experimental Group.** The individual case histories and protocols of the dogs are noted below.

**Protocols.** Dog 6. Male hound. *Duct injection. Death in 12 hours.*

Friday, February 27. Right and left ducts were injected with 2 cc. of a 24-hour broth culture of hemolytic *Staphylococcus aureus* of high virulence. The left duct was ligated; the right one not.

Saturday, February 28. Autopsy revealed no signs of frank inflammation or suppuration.

**Microscopic Findings.** *Right gland (unligated duct):* The section of this gland shows many areas of cellular infiltration (chiefly neutrophils), suppuration, and necrosis. The exudate is noted in the parenchymatous tissue, but more especially in the ducts, and tissue immediately surrounding the ducts. The larger ducts show greatest degree of involvement and destruction of epithelial lining.

\* The culture of low virulence failed to kill a rabbit in 5 days under similar conditions.

Destruction of the glandular tissue is widespread and varies in degree from cloudy swelling to complete necrosis. Some few areas of the tissue are perfectly normal.

*Left gland (duct ligated):* The picture is the same as above but more widespread; the degeneration of parenchymatous tissue is so marked that relatively few gland cells are evident and the necrosis of the lining of the ducts is much more severe.

**Dog 5.** Male hound. *Duct injection. Death in 12 hours.*

Friday, February 27. The right duct was injected with 2 cc. of a 24-hour broth culture of hemolytic *Staphylococcus aureus* of high virulence; the duct was ligated.

February 28. Autopsy revealed no gross evidences of inflammation.

*Microscopic Findings.* The section from this gland shows widespread infiltration by polymorphonuclear leukocytes and a few round cells throughout the parenchyma, especially in the ducts and periductal tissue; the destruction of the glandular tissue has advanced to such an extent that in no area can normal structure be recognized. There is no involvement of the bloodvessels. Most of the ducts are greatly distended with purulent exudate; in some places the epithelial lining of the ducts shows breaks which result in a flooding of surrounding glandular tissue with exudate.

**Dog. 644.** Female hound. *Duct injection. Death in 36 hours.*

February 27. An injection was made into both ducts of 2 cc. of a 24-hour broth culture of hemolytic *Staphylococcus aureus* of high virulence.

The left duct was ligated; the right one not.

March 1. The dog died during the preceding night.

March 2. Autopsy showed no gross indications of suppuration or inflammation.

*Microscopic Findings. Right gland (duct unligated):* There is no sign of inflammation; there are no leukocytes in the ducts or other parts of the gland. The tissue appears normal throughout.

*Left gland (duct ligated).* The larger ducts are filled with a cellular exudate consisting of many polymorphonuclear leukocytes and a few round cells. There is cellular infiltration into the periductal tissue; these areas show almost complete necrosis with little of the glandular element remaining. Some portions of the gland appear normal.

The bloodvessels are normal.

**Dog. 784.** Female fox terrier. *Duct injection. Death in 4½ days.*

March 9. Injected Stensen's duct on each side with 1 cc. saline suspension of stock culture of hemolytic *Staphylococcus aureus* of low virulence. Both ducts were ligated after the injection was made.

During the following 5 days the dog showed symptoms of a progressive toxemia, becoming gradually more lethargic and weak.

March 14. The dog died during the preceding night having survived the injection 4½ days.

At autopsy there was moderate suppuration of the left gland and its duct, and extensive suppuration of the right. On section of the latter gland considerable quantities of pus could be expelled.

*Microscopic Findings. Right gland.* Most of the parenchyma is involved in the suppurative process. The walls of many of the largest ducts are decidedly necrotic; many whole lobules of the gland appear as small abscesses centering about their ducts.

A few of the lobules appear normal except for the presence of cellular exudate in the ducts.

*Left gland.* The same picture is seen here as in the right gland, except that the periductal infiltration and necrosis is less marked.

**Dog. 673.** Male terrier. *Arterial injection. Death in 12 hours.*

Friday, February 27. The right superficial temporal artery was injected

with 2 cc. of 24-hour broth culture of hemolytic *Staphylococcus aureus* of high virulence.

Saturday, February 28. Death occurred in 12 hours. Autopsy showed no gross evidences of inflammation or suppuration.

*Microscopic Findings.* There were no signs of inflammation, no hemorrhage, no leukocytic infiltration of any type, no areas of glandular necrosis, no evidences of bacteria in the ducts, vessels or alveoli. The tissue appeared entirely normal.

**Dog 693.** Male hound. *Arterial injection. Death in 36 hours.*

Friday, February 27. The injection of 2 cc. of a 24-hour broth culture of hemolytic *Staphylococcus aureus* of high virulence was made into the right superficial temporal artery.

Sunday, March 1. The dog died during the preceding night.

Monday, March 2. Autopsy revealed patchy consolidation of both lungs. The right parotid gland was removed and inspected; no signs of inflammation or suppuration were seen.

*Microscopic Findings.* The glandular tissue shows no signs of suppuration or inflammation. There are no evidences of bacteria in or surrounding the ducts.

The periglandular connective tissue shows marked hyperemia with some hemorrhage.

**Dog 782.** Female terrier. *Arterial injection. Death in 4 days.*

March 26. The right superficial temporal artery was injected with 2 cc. of 24-hour broth culture of hemolytic *Staphylococcus aureus* of high virulence.

March 30. During the 4 days following injection, the dog grew progressively weaker. The animal was chloroformed today. Both parotid glands were removed and inspected. Neither exhibited any gross manifestations of suppuration or inflammation.

*Microscopic Findings. Right gland.* In general the glandular tissue is free from any evidence of inflammation. However, a number of areas about the smaller ducts show a limited infiltration with lymphocytes and macrophages, but no necrosis of glandular tissue. Several large ducts contain a few polymorphonuclear leukocytes. Throughout the section small blood-vessels are noted in which the endothelial lining appears hyperplastic and swollen. In the lumens of these vessels erythrocytes are adherent to the intima, in some cases appearing to have broken down, forming an annular hyalinized mass, possibly representing early thrombi.

*Left gland.* There are no areas of suppuration or necrosis. There are occasional monocytes in the tissue surrounding some of the larger ducts. A few of the ducts contain an occasional polymorphonuclear leukocyte.

**Dog 910.** Female collie. *Arterial injection. Death in 5 days.*

Friday, April 10. The right superficial temporal artery was injected with 1 cc. of a 24-hour broth culture of mixed hemolytic *Staphylococcus aureus* and *Pneumococcus* obtained from a human case of acute suppurative parotitis.

Wednesday, April 15. The dog, apparently in good condition, was chloroformed and autopsied. The right parotid gland was removed. There was no evidence of inflammation or suppuration on gross inspection.

*Microscopic Examination (Frozen section).* There were no inflammatory changes noted in the gland.

**Dog 898.** Male police dog. *Arterial injection. Death in 7 days.*

Friday, April 10. The right superficial temporal artery was injected with 1 cc. of a 24-hour culture of *Staphylococcus aureus* and *Pneumococcus* (as in No. 910).

Friday, April 17. Dog in good condition. Chloroformed and autopsy performed; inspection of the right gland revealed no gross manifestations of inflammation or suppuration.

*Microscopic Examination.* The frozen section in this case showed a gland apparently normal in all respects; no evidence of parenchymatous degeneration or leukocytic infiltration was noted.

**Dog 807.** Male shepherd. *Arterial injection. Death in 7 days.*

Wednesday, March 25. Given 30 cc. of castor oil, and placed on a solid diet with no liquid intake.

Thursday, March 26. The right superficial temporal artery was injected with 2 cc. of a broth culture of hemolytic *Staphylococcus aureus* of high virulence. The operation was not wholly successful, due to difficulty in injecting an unusually small artery. The procedure was repeated on the opposite side.

Thursday, April 2. The dog died during preceding night, 7 days after the injection. At autopsy, both parotids were removed, neither one showing any gross evidences of suppuration or necrosis.

*Microscopic Findings. Left gland.* No inflammation, no necrosis, no suppuration. *Right gland,* normal, no inflammatory changes.

**Dog 7.** Shepherd. *Arterial injection. Death in 8 days.*

February 27. Both right and left superficial temporal arteries were injected with 2 cc. of 24-hour broth culture of hemolytic *Staphylococcus aureus* of high virulence.

March 6. During the first 3 days following the injections the animal appeared toxic, after which a gradual improvement was noted. Today appears in good condition.

March 7. The dog was chloroformed. At autopsy both the right and left glands were removed and inspected. No gross evidences of suppuration were noted.

*Microscopic Findings. Left gland.* Three adjacent lobules show a quite marked inflammatory process. The ducts contain many polymorphonuclear neutrophils. The epithelial lining of these ducts is intact except at a few points where leukocytes are passing between the epithelial cells apparently engaged in diapedetic movement toward the lumens of the ducts. Neutrophils are seen but rarely in the periductal tissue except in areas between vessels and ducts. In the periductal parenchyma there are large numbers of monocytes and lymphocytes. In these areas there are but few signs of necrosis of the glandular tissue.

The endothelial lining of the bloodvessels shows some swelling, and hyperplasia. Many of the erythrocytes in the lumens of the vessels are adherent to the intima. A few polymorphonuclears are seen in the lumens of the vessels.

The remainder of the gland is normal except for a scattered round-cell infiltration.

*Right gland.* There is one small area composed of several lobules that show inflammation even more marked than that in the left gland. The same characteristics are seen: slight hyperplasia of the endothelium of the vessels, migration of polymorphonuclears from the vessels toward the adjacent ducts, a small number of polymorphonuclears in the ducts, very few polymorphonuclears throughout the glandular tissue, little necrosis or degeneration of glandular tissue, no abnormalities in the epithelium of the ducts, and widespread periductal infiltration with monocytes and lymphocytes (Figs. 3 and 4).

**Dog 760.** Male shepherd. *Arterial injection. Death in 12 days.*

Wednesday, March 25. The dog was placed on a solid diet with no water for 24 hours preceding operation. A dose of 30 cc. of castor oil was administered orally.

Thursday, March 26. An injection of 2 cc. of a 24-hour broth culture of hemolytic *Staphylococcus aureus* was made into the right superior temporal artery. The bacteria were of high virulence.

Tuesday, April 7. The animal was chloroformed and autopsied. Both right and left parotid glands were removed and inspected. No gross signs of suppuration or inflammation were noted.

*Microscopic Findings.* *Left gland* (uninjected). Histologically normal. *Right gland* (injected). Histologically normal.

**Dog 814.** Male fox terrier. *Arterial injection.* *Death in 14 days.*

Thursday, March 26. The right superior temporal artery was injected with 2 cc. of a 24-hour broth culture of virulent hemolytic *Staphylococcus aureus*.

Thursday, April 9. The dog was chloroformed and autopsied. The right parotid gland showed no gross indication of any pathologic change.

*Microscopic Findings.* No indications of inflammatory change; gland is normal in all respects.

**Discussion of First Experimental Group.** All but one of the glands injected with bacteria through the ducts showed marked suppuration; two of the eleven arterial injections resulted in recognizable inflammation.

In the series of seven duct injections five were ligated. The histologic picture in all of these five was identical, varying only in degree of inflammation. The ducts were distended with a purulent exudate, most extensive in the larger channels, gradually lessening in amount as the finer radicals were approached. At many points the duct walls were destroyed and the suppurative process extended into the surrounding glandular tissue. The cells of the intraductal exudate were almost exclusively neutrophils; of the periductal exudate there was an intermingling of monocytes and lymphocytes. The glandular tissue showed extensive degeneration and necrosis, in 1 case actual abscess formation. The bloodvessels showed no changes.

Two duct injections were not followed by ligation of the ducts. One of these glands showed an acute suppurative process similar to and quite as extensive as seen in the cases in which ligation was performed. There was no evidence of inflammation, however, in the second.

Nine of the glands the nutrient arteries of which were injected with bacteria showed no pathologic changes, except for a slight round-cell infiltration and vascular endothelial hyperplasia in 1 case (Dog 782). In each parotid of Dog 7, after a bilateral arterial injection, there was a marked inflammatory reaction, locally limited to several lobules. Here the inflammation was periductal, characterized by an extensive mononuclear infiltration. The smaller ducts contained neutrophilic exudate, but there was no destruction of the lining epithelium. The large ducts appeared normal. The intima of the arterioles showed swelling and hyperplasia.

From this series it is evident that the parotid gland is more readily infected through its duct than through the blood stream and that the pathologic picture in each mode of infection is not identical.

**Second Experimental Group.** In this group of 7 animals variations of the previous procedures were performed, as well as repetition of

the methods used in the first group in several instances. It was thought advisable to note the effect of simple ligation of the duct without injection. To determine whether the local resistance of the gland was lowered sufficiently by bacterial toxins to allow ascent of infection from the mouth, the arteries were injected with a filtrate of 5-day bacterial growth. To provide a coarse suspension of bacteria for injection into the arteries the organisms were agglutinated by incubation in serum before use. An arterial injection was made in a gland, the duct of which was ligated. In the same animal the opposite duct was injected with bacteria. In addition, a simple arterial injection and an unligated duct injection was performed as before.

The results of these procedures are noted in the individual animal records noted below:

**Protocols. Dog 1099. Arterial injection. Death in 9 days.**

June 2. A bilateral injection of 2 cc. of a 24-hour broth culture of hemolytic *Staphylococcus aureus* of high virulence was made into the superficial temporal arteries.

June 11. Autopsy performed. No gross suppuration noted in either gland.

*Microscopic Findings. Right gland.* Shows a slight mononuclear infiltration about some of the smaller ducts, but appears normal otherwise.

*Left gland.* There is an extensive subacute inflammatory reaction throughout the gland, centering about the smaller ducts, in general. Much of this periductal exudate is mononuclear. The smaller ducts contain clumps of polymorphonuclear leukocytes and show slight hyperplasia of the lining epithelium. The larger ducts contain no exudate and their walls are intact. The arteriolar endothelium is hyperplastic. *These changes are pictured in Fig. 2; they are characteristic of hematogenous parotitis.*

**Dog 1098. Unilateral arterial injection with ligated duct. Death in 2 days. Unilateral duct injection with duct ligated.**

June 2. The artery of the right gland injected with 2 cc. of a 24-hour broth culture of hemolytic *Staphylococcus aureus* of high virulence. The duct of the gland ligated.

The duct of the left gland injected with 2 cc. of the same culture and the duct ligated.

June 4. Autopsy performed. No gross suppuration noted in either gland.

*Microscopic Findings. Right gland.* There is moderate desquamation of the epithelial lining of the ducts but no evidence of inflammation.

*Left gland.* The ducts are filled with a purulent exudate, most marked in the larger branches, less in the terminal branches. The epithelial lining of the former is markedly damaged, in some places completely desquamated, in others flattened and degenerated. The periductal tissue shows moderate infiltration by neutrophils and a few mononuclear cells. The glandular elements are slightly degenerated, but the process has not proceeded to actual necrosis and abscess formation as seen in several earlier cases. The bloodvessels show no changes. *Fig. 1 shows the histologic picture seen in this gland; it is characteristic of the early changes in ductogenous parotitis.*

**Dog 700. Bilateral duct ligation. No injection. Death in 4 days.**

June 1. The ducts of each parotid gland ligated.

June 5. Autopsy performed. No gross changes noted in either gland.

*Microscopic Findings.* The right gland shows slight hyperplasia and degeneration of the lining epithelium of the ducts with suggestion of desquamation. The left gland appears normal histologically. No inflammatory change is noted in either.

**Dog 1104.** Bilateral arterial injection of bacterial filtrate. *Death in 1 day.*

June 4. The artery to each parotid gland injected with 2 cc. of a Berkeley filtrate of a 5-day broth culture of virulent hemolytic *Staphylococcus aureus*.

June 5. Autopsy performed. No changes noted in either gland.

*Microscopic Findings.* The histologic picture in each gland was normal.

**Dog 1081.** Bilateral arterial injection of bacterial filtrate. *Death in 7 days.*

June 4. Procedure similar to 1104 performed.

June 11. Autopsy performed. Neither gland showed any gross change.

*Microscopic Findings.* No evidence of inflammation or degeneration is seen in either gland.

**Dog 984.** Bilateral arterial injection of agglutinated bacteria. *Death in 9 days.*

June 8. Each superficial temporal artery injected with 2 cc. of a 48-hour broth culture of hemolytic *Staphylococcus aureus* that had been incubated for 24 hours with equal parts of dog serum, producing definite flocculation.

June 17. Autopsy performed. Each gland appeared grossly normal.

*Microscopic Findings.* No histologic change can be seen in either gland.

**Dog 631.** Bilateral duct injection without ligation. *Death in 7 days.*

June 1. The duct of each parotid gland was injected with 2 cc. of a 24-hour culture of hemolytic *Staphylococcus aureus* of high virulence. The ducts were not ligated.

June 8. Autopsy performed. No evidence of inflammation noted in either gland.

*Microscopic Findings.* Neither gland showed histologic evidence of inflammation.

**Discussion of Second Experimental Group.** In this group further evidence has been obtained that the histologic picture in hematogenous and in ductogenous parotitis is not identical. This is clearly illustrated in Figs. 1 and 2 and discussed in the protocols of Dogs 1098 and 1099. It has been shown that simple ligation of the duct of the parotid gland is followed by no inflammatory change in a period of 4 days; that injection of bacterial filtrate does not lower the resistance of the gland sufficiently to permit invasion by organisms resident in the mouth and in Stensen's duct; that injection of clumped bacteria did not produce inflammatory changes in the glands.

**Summary.** In 7 instances out of 10 following injection of bacteria into Stensen's duct acute suppurative parotitis was produced. On the other hand, in 3 instances out of 15 following injection of bacteria into the nutrient artery of the parotid gland an acute suppurative parotitis of much less intensity was produced. In 2 other of these 15 cases a slight mononuclear infiltration was noted. Single controls of ligation of the duct alone, injection of bacterial filtrate and of clumped bacteria into the artery did not produce parotitis.

The histopathologic picture differs in glands infected through the duct and through the blood stream, as tabulated below:

#### Ductogenous parotitis.

1. Distention of ducts with purulent exudate.
2. Large ducts involved most extensively, small radicals least.
3. Extensive destruction of duct epithelium.
4. Periductal reaction most prominent where duct wall is broken.
5. Periductal cell reaction chiefly neutrophilic.
6. No changes in bloodvessels.

#### Hematogenous parotitis.

1. Purulent exudate in ducts less marked. Ducts not distended.
2. Large ducts relatively unchanged. Small radicals chiefly involved.
3. Epithelial lining of ducts intact, or occasionally hyperplastic.
4. Periductal reaction more uniform in distribution.
5. Periductal cell reaction chiefly mononuclear.
6. Swelling and hyperplasia of arteriolar endothelium with occasional beginning annular thrombus formation.

**Conclusions.** 1. Acute suppurative parotitis can be produced by injection of bacteria into Stensen's duct, or by injection of bacteria into the nutrient artery of the parotid gland.

2. Infection of the gland is produced with much greater facility through the duct.

3. The histopathologic picture in the 2 cases is dissimilar.

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### ACUTE SUPPURATIVE PAROTITIS.

#### A PATHOLOGIC AND BIBLIOGRAPHIC STUDY WITH REPORT OF TWO CASES.

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SINCE the first accurate pathologic study of acute suppurative parotitis by Virchow, in 1858, one finds many additional descriptions of the pathological anatomy as well as clinical discussions of this disease.



The condition is one of great practical significance because it not infrequently follows surgical operations and occurs during the course of infectious diseases and debilitating conditions and occasionally develops primarily. The mortality is usually high, being estimated by Wagner at 30 per cent, by Blair and Padgett at 42.8 per cent.

The divergence of opinions held by the various authors appears to be confined to one question, *viz.*, the route of infection. Most observers hold that the invading organism ascends through the ducts, secondarily invading the gland tissue; others that the source of infection is hematogenous. The possibility of lymphogenous infection from the nose and throat has also been mentioned. Infections of the gland by extension from surrounding structures are obvious and deserve mere mention. Of the relative merits of each of these views, more will be said later.

**Case Reports.** CASE 1.—J. A., a white male, aged 22 years, was admitted to the medical service of the Allgemeines Krankenhaus of Innsbruck on May 2, 1930, complaining of abdominal pain, bloody diarrhea, and headache. During the month previous to admission he noted loss in weight and a progressively increasing weakness, the latter becoming so pronounced that he was unable to continue work. This was followed by severe diarrhea with generalized abdominal pain and intense headache. Defecation was extremely painful and the stools were bloody.

Shortly before the onset of the present illness the patient had been treated in the Dermatologic Clinic for chronic eczema but had not been given mercury nor arsenic. Other than this, the personal history contained nothing of interest.

The family history noted tuberculosis in immediate relatives but was otherwise negative.

Physical examination on admission showed a well developed but undernourished young adult male who appeared quite ill. The head and neck were negative; the teeth ill-kept and carious. The heart and lungs were normal. Abdominal examination revealed generalized tympany without rigidity, local or generalized tenderness. The spleen was palpably enlarged. There were no other findings of significance.

The urine contained a cloud of albumin, hyalin casts and many red and white blood cells. The hemoglobin was 61 per cent, red cell count 4,410,000, and white cell count 18,800. The differential count showed 78 per cent polymorphonuclear leukocytes, of which 14 per cent were young forms. The stools were hypocholic and bloody. Study of the sputum, urine and stool was negative for *Bacillus tuberculosis*. Sigmoidoscopy revealed nothing but acute inflammation of the mucosa.

The patient appeared to improve until May 9, from which time his condition grew gradually worse. He did not tolerate even liquid diet and consequently the fluid intake was small. The urine showed great numbers of hyalin casts and an increasing amount of albumin, finally reaching 12 per cent (Esbach). The total white cell count remained constant but the polymorphonuclears fell to 43 per cent and the young forms to 3 per cent. There was a corresponding increase in lymphocytes to 46 per cent. Fever had not been a particularly marked feature, but on May 29 the temperature rose to 38° C. and swelling and tenderness of the right parotid gland first appeared. The swelling in the parotid region rapidly increased, the temperature mounted and the patient died May 31.

It is of interest to note that the etiology of the enteritis could not be determined. Many clinicopathologic studies were performed during life and a careful bacteriologic examination was made of a sealed loop of small intestine removed at autopsy. All of these tests were negative for a causative factor. It was considered finally to be secondary to the nephrosis, *i. e.*, the so-called "uremic enteritis."

*The autopsy* (No. 19163/219) showed basal bronchopneumonia with moderate bilateral hydrothorax; myocardial degeneration and hydropericardium; acute, necrotic, hemorrhagic enteritis with marked hyperplasia of the mesenteric and paravertebral lymph nodes; passive congestion and early amyloid change on the liver; splenomegaly; extremely marked amyloid nephrosis. In the buccal mucosa were aphthous ulcers and the tonsils were inflamed.

*The right parotid gland* was enlarged and firm, the cut surface being mottled yellow and gray. Hemorrhage in the trabeculae was evident. Purulent exudate could be expressed from the larger ducts.

*The histologic picture* of the parotid gland was clear-cut because the condition had existed clinically but 2 days. Diffuse necrosis and suppuration has not yet occurred.

*The changes in and about the ducts* constitute the chief lesion in this case. The severity of the process is most marked in the larger ducts, the smaller radicals being least involved. The ducts in general are filled with a purulent exudate, the larger being distended to such an extent that the epithelial cells are quite flattened. Where the epithelial lining of the ducts maintains its continuity, the periductal necrosis and cellular infiltration is slight or absent. However, at many points destruction of the epithelium has occurred and through these gaps the infection has penetrated into the surrounding glandular tissue (Fig. 2). Fig. 1 gives an excellent topographic view of the picture seen throughout the gland. The inflammatory cells present within the ducts are polymorphonuclear leukocytes, while the cellular collar about the ducts is composed mostly of large mononuclears.

In some of the larger ducts, colonies of bacteria are seen in the hematoxylin-eosin preparations, particularly in those ducts where the infection is most intense. When sections are stained by the Gram method, smaller numbers of bacteria are visible in all of the ducts, but the glandular tissue is bacteria-free. Unfortunately, cultures from the gland were not taken at autopsy, but the organisms, from their morphology and manner of colonization in the tissue, appear to be staphylococci.

*The glandular tissue* is not constantly involved in the inflammatory process. In many situations the parenchyma about the pus-filled ducts is normal, except for a slight infiltration with mononuclear wandering cells. In these ducts, the lining epithelium is always intact.

When the epithelium of the duct is destroyed, the infection spreads to the adjacent glandular tissue, this latter tissue is infiltrated with mononuclear cells and ultimately undergoes necrosis. In general, however, the destruction of glandular elements is relatively slight.

*The changes in and about the vessels* are inconspicuous (Fig. 3). Where the vessels lie in close proximity to an infected duct, a cellular exudate is present about them. This exudate is usually mononuclear and the cells are accumulated along the side of the vessel adjacent to the duct. The veins contain many leukocytes, chiefly in a marginal position. There are no thromboses nor infarcts.

*In the stroma* the most conspicuous feature is extensive hemorrhage, such extravasations being found in the larger trabeculae. Extension of the infection into the connective tissue about the larger ducts has occurred following destruction of the epithelial lining (Fig. 4).

CASE 2.—M. S., a white female, aged 54 years, was admitted to the medical service of the Allgemeines Krankenhaus of Innsbruck on May 15,

1930, complaining of pain, swelling and redness of the left foot and leg, chills and fever. Four days before admission, the area about a previous slight injury suddenly became inflamed and the process extended to the knee within the next 3 days, the margin being sharply demarcated. The foot and leg were swollen, bright red in color and extremely painful. General febrile reaction was pronounced.

The personal and family histories were negative.

The important physical findings were the typical lesion of erysipelas involving the left foot and leg, ending abruptly at the knee. The heart was enlarged to the left and there were basal râles in both lungs. The mouth was extremely dry and aphthous ulcers were present in the buccal mucosa.

The leukocyte count on admission was 16,200. The blood cultures were sterile.

The inflammatory process rapidly extended to the left thigh and buttock and, on May 22, the left parotid gland became swollen tense and painful. The leukocyte count rose to 32,000 (88 per cent polymorphonuclears). The parotitis became more intense and the patient's general condition grew rapidly worse. She died May 27, 5 days after the onset of the parotitis.

At autopsy the chief pathologic findings, aside from the lesion of erysipelas in the left lower extremity, were hypertrophic fatty heart, acute pulmonary edema, fatty liver, nephrosis and general arteriosclerosis.

Over the left parotid region were pus-filled blebs and the gland itself showed suppurative softening. The cut surface was mottled and pin-head sized areas of abscess formation from which pus exuded were seen.

The microscopic findings are not so definite as in Case 1, as the process has proceeded to more definite necrosis and abscess formation. However, a certain amount of information is gained from histologic study.

The ducts appear to be the center of the infectious process and the more advanced abscesses center about the large radicals. Great clumps of bacteria are visible in the ducts (Fig. 5) and in many places the bacterial growth extends into the surrounding glandular tissue with necrosis and liquefaction of the latter. As in Case 1, the organisms are Gram-positive cocci that appear morphologically to be staphylococci. Sections from the skin and subcutaneous tissue of the left thigh show Gram-positive cocci in chains, having a tendency to spread diffusely rather than clump, suggesting streptococci.

The parenchymal elements are all involved in varying degrees but the degeneration and necrosis becomes more marked as the center of the lobule is approached.

As before, the vessels are relatively unaltered and there are no thromboses nor infarcts.

The stroma does not show the hemorrhage as in Case 1, but a moderate degree of edema and mononuclear cell infiltration are present, particularly in the fibrous elements that support the main ducts.

**Summary of Case Reports.** Case 1 demonstrates the occurrence of acute suppurative parotitis during the course of amyloid nephrosis with hemorrhagic enteritis. The infectious process in the gland centers about the ducts and the causative organism appears morphologically to be a staphylococcus. The etiology of the enteritis was apparently nonbacterial and the clinical picture was not that of staphylococcus septicemia.

Case 2 presents the complication of acute suppurative parotitis

occurring with erysipelas of the leg. Here, also, the inflammation centers about the ducts and the bacteriologic findings in the tissue of the gland and of the leg are dissimilar.

In each case the bloodvessels show no damage and there are no thrombotic nor embolic lesions.

**Literature.** Virchow, in 1858, studied a series of 18 cases of acute parotitis. He described small abscesses in the wall of Stensen's duct and believed the infection to be ductogenous. The glandular epithelium he observed to have undergone first a fatty degeneration; later actual necrosis. Further stages of the infectious process he describes thus: "Die Drüsenläppchen durch eine Erweichung, eine Art von Schmelzung, welche ihre Produkte mit dem Eiter der Kanäle mischt und leicht den Eindruck macht, als seien die Drüsenkörnchen direkt in kleine Abszesse umgewandelt zerstört."

Previous to this work the gross pathologic picture of the condition had been described best by Sir Benjamin Brodie, in 1834, who stated: "On opening the body after death matter is found deposited in small portions throughout the interstitial substance of the gland itself and specks of matter appear here and there, poured out on pressure from various parts."

Rindfleisch (1878), after microscopic study of acute parotitis occurring during infectious diseases, remarked that the larger ducts were distended with pus and the finer radicals and acini were filled sometimes with swollen glandular epithelium and sometimes with leukocytes (with or without necrosis of the desquamated epithelium). Later, suppuration occurred, sometimes to the extent that the entire gland was converted into a large abscess.

Wendt (1880) observed the inflammatory process to begin with a hyperemia, edema and exudation of red and white blood cells in the stroma about the glandular elements. The next change occurred in and about the ducts; these were filled with a purulent exudate and desquamated duct epithelium. Later, the glandular elements themselves became involved in the necrotic process, together with the connective tissue.

Orth (1887) made similar observations noting the first changes to be in the ducts, the glandular and connective-tissue changes occurring secondarily.

Hanau (1889) noted that the walls of the larger ducts that run through the fibrous septa of the gland were infiltrated with leukocytes and the epithelial lining cells was flattened by distention with purulent exudate containing cocci. As the process proceeded, the destruction of the duct walls became so marked that the identity of the structures was lost. The small intralobular ducts were later involved and became the center of intralobular abscesses which coalesced and large abscess cavities were formed.

Nicol (1912), in a series of 5 cases, noted the beginning of the

infectious process in the large ducts and its spread throughout the smaller radicals, finally including the secretory elements proper. He observed also the presence of cocci in the exudate in the ducts, but was unable to demonstrate organisms in the gland tissue.

Heineke (1913) referred to the findings of the preceding authors and others and supplemented them with his own observations. He concluded that, with very few exceptions, the evidence favored the view of ascending infection.

Bonnet-Roy (1921), as well, remarked that the changes centered mostly about the ducts.

Analogies have been drawn between infection of the parotid gland and suppurative processes in similar anatomic structures. Klebs, for example, mentions ascending infection through the ureter with production of pyelonephritis (as does Nicol), and Bumm believes the occurrence of puerperal mastitis and sebaceous gland furuncles to be like processes.

Many authors have commented upon the condition from a bacteriologic standpoint. Bacteria have been demonstrated in the larger ducts under physiologic conditions (Galippe, Ginner, Cornil and Ranvier) but not in the middle-sized and small radicals, nor in the gland tissue proper. The likelihood of the propagation and increase in virulence of these organisms and their dissemination through the gland, concomitant with lowered resistance of the body through general illness, or of the gland alone through trauma, has been thought quite probable.

Most observers who have studied the bacteriology of the exudate and tissue of the infected parotid gland have not been able to correlate their findings with the bacteriology of the general illness except in rare instances (Dunin, Heineke and others). This positive correlation is most frequent in typhoid fever (Janowski) and has been occasionally seen in gonorrhea (Colombini, Power, Wittwer). The chief findings, however, have been staphylococci, streptococci, diplococci and bacillus coli.

F. J. Lang (1929), after an exhaustive review of the literature and a survey of a number of his own cases, has concluded that the anatomic and bacteriologic evidence favors the view of ascending infection in nearly all instances.

Boyd says: "The infection may come from the blood stream, as in acute fevers or in pyemia, or from the surrounding structures. Infection from the mouth by way of Stensen's duct is the most obvious and important method. The most frequent invaders are the staphylococcus aureus and the pneumococcus."

Two cases have been reported in which anatomic findings would suggest hematogenous infection. The first of these (Sabrazes and Faguet, 1894) was the instance of complete suppuration of a lobule of the parotid with absence of pus in Stensen's duct. In the second (Roberts, cited by Claissé and Dupré, 1894) the parotid veins and

veins in the neck were filled with pus. In neither case was histologic study made and Rost has dismissed them as questionable evidence on this account.

On the other hand, Küttner believes the hematogenous origin of the infection to be far more common than is ordinarily supposed and does not think anatomic findings to be sufficient evidence in favor of the previous view.

Orth, in a later paper (1894) drew attention to a form of hematogenous suppurative nephritis in which the organisms passed through the glomeruli and set up an inflammatory process in the collecting tubules. He thought that an analogy might be drawn between this phenomenon and that of suppurative parotitis.

This latter view is supported by the experimental work of Rost (1914). He injected pure cultures of bacteria into the internal maxillary artery (the blood supply of the parotid) of dogs and removed the glands between the third and fourteenth day. He found that the ducts alone were filled with pus and that no suppurative thrombosis nor embolism had occurred. Injection of the artery showed an extremely rich blood supply of the gland and upon this factor depended the rapid production of pus in the ducts. From this work he concluded that there was no difference in the anatomic picture between infection of the gland through the ducts and through the blood stream. Similar experimental studies by Berndt, Buck, Buxton and the writer were performed and are reported in this issue (page 639). They will be discussed later.

Dawydowskie, after a study of parotitis complicating typhus, believed that the lymphogenous route of infection from the nasal cavity is quite possible, as well as the ascending route.

The literature holds accounts of *a wide variety of conditions* with which acute suppurative parotitis has occurred.

Undoubtedly as a result of the interrelation of the parotid and the testicle and ovary in mumps that has been noted since the first observation by Hippocrates came the thought that the nonspecific inflammation of the gland bore the same relation. This view was championed chiefly by Munde, Möricke and Goodell, who individually reported, between the years 1878 and 1881, a number of cases of parotitis following operations on the female genitalia. Subsequent observations have shown this idea to be fallacious.

In the surgical field parotitis has been seen principally following abdominal operations, most especially after those performed in septic areas, for example, in suppurative appendicitis, cholecystitis, gastric and urologic operations, etc. (Wagner, Heineke, Hanau, Orthner, Oehler, Valentin, Möricke, Sinnecker, Clairmont and others). These authors, especially Heineke, believe that the ascending route of infection is more likely, except Wagner, who thinks both ascending and hematogenous infections possible. Tebbs, Wittwer, Silbermann and Kagan and others are advocates of the hematogenous theory.

In *nonsurgical conditions* parotitis has been observed during the course of many acute and subacute infectious diseases.

*Typhoid fever* stands in the foreground (Curschmann, Hoelscher, Mallory, Christeller), the parotitis appearing mostly as a unilateral involvement, but occasionally occurring bilaterally (Henke, Cahanescu). It is most often a suppurative process (Rokitansky, Hoffmann), but rarely appears as a hard, diffuse, interstitial, nonsuppurative inflammation (Henke). Bacteriologic study of the gland in typhoid fever has sometimes showed the presence of bacillus typhosus alone (Janowski), but the more frequent findings have been staphylococci and streptococci (Dunin, Fraenkel and Simmonds, Fraenkel, Bonardi, Flora e Silverstrini, Anton and Fütterer, Curschmann, Schottmüller and others). Anton and Fütterer found staphylococci and streptococci together with bacillus typhosus.

*Typhus fever* is not uncommonly complicated by parotitis (Dawydowskie, Werzblowski, Herzen, Zlocisti, Ceelen). These writers, in general, present evidence in favor of ascent of infection through the ducts.

Heineke mentions a number of cases of purulent inflammation of the parotid occurring with *lobar pneumonia*, in some of which pneumococci as well as staphylococci were found in the purulent exudate. Seifert, however, does not think that this is evidence in favor of hematogenous infection, as the pneumococcus occurs in the normal bacterial flora of the mouth.

The other infections with which the condition has been described are scarlet fever, diphtheria, variola, cholera, dysentery (Beitzke), glanders, malaria (McWalter, Seyfarth), plague, influenza, erysipelas, puerperal sepsis, infectious arthritis, appendicitis (Fiske), tuberculosis, tularemia (E. Francis) and Dengue fever (Kondoleon and Joannides), occurring either unilaterally or bilaterally.

Blair and Padgett (1923) analyzed a series of 35 cases of acute pyogenic parotitis from a clinical point of view. They conclude that the condition is, in the great majority of cases, an ascending infection from the duct related to decreased salivary flow, fever and depressed general condition. Three of their cases presented evidence that the infection may have been blood-borne, but they state that absolute proof is lacking. Likewise, 1 case suggested the possibility of lymphogenous transmission from an infected wound of the forehead. They also make the interesting observations of predominant occurrence after the third decade and most frequent incidence between the months of November and April, when respiratory infections are most common. Pneumonia was present in 11 cases and 4 others gave a history of preceding "cold." One-fifth of their cases were bilateral. The most common infecting organism was a staphylococcus and the mortality was 42.8 per cent.

Parotitis not infrequently complicates *chronic debilitating conditions*, for example, chronic kidney disease, cirrhosis of the liver,



FIG. 1.—View of several lobules showing purulent exudate in the ducts, a collar of mononuclear cells about the ducts and hemorrhage in the interlobular trabeculae. (Case 1.)

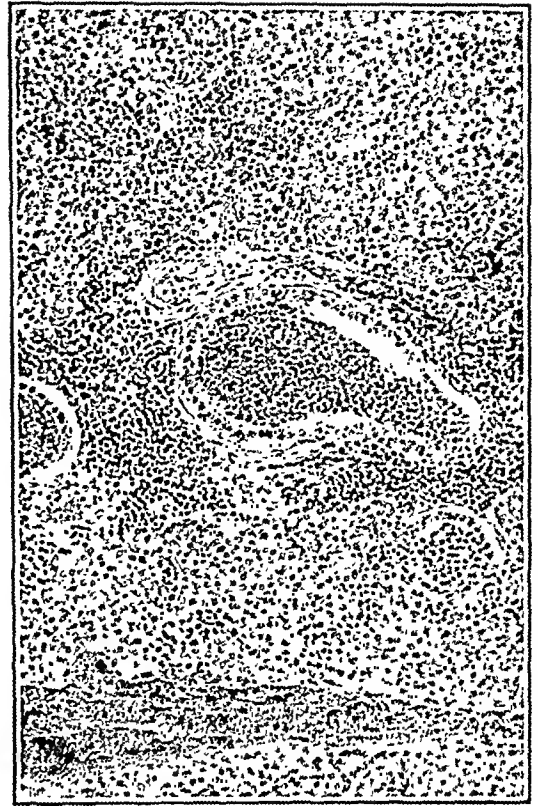


FIG. 2.—High power of outlined field in Fig. 1, showing a break in the duct epithelium and extension of infection into the periductal tissue. (Case 1.)

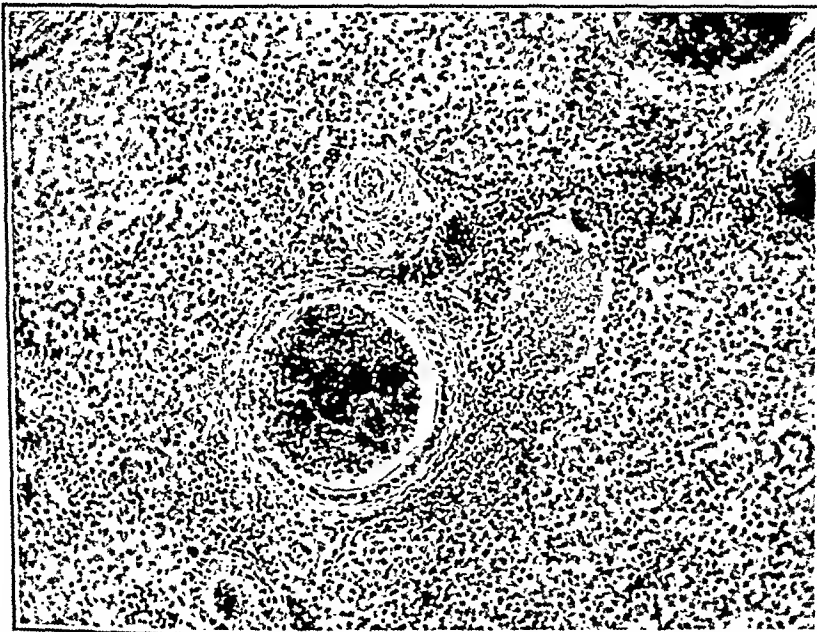


FIG. 3.—Relatively intact arteries and a vein with inflammatory cellular exudate chiefly adjacent to the duct. (Case 1.)





FIG. 4.—Large branch of Stensen's duct, showing extension of infection into the supporting connective tissue. (Case 1.)



FIG. 5.—Early abscess, the center of which is a bacteria-filled duct. (Case 2.)

cardiac disease, anemias (Fuhr), cachexia of malignancy, diabetes mellitus, paralyses, leukemias (Bickhardt, Heineke, Gigon and others) and advanced senility (Etienne) usually terminating fatally. Etienne noted that in senility the submaxillary and sublingual glands were more frequently involved than the parotid. Bickhardt described a case of parotitis occurring with lymphatic leukemia, in which the cells of the purulent exudate from the gland were exclusively lymphocytes.

Suppurative inflammation of the parotid has been observed in the *newborn* and in *suckling infants* (Decker). Plewka described 1 case and collected reports of 42 other cases in the literature, as well as 9 in which the other salivary glands were affected. Mikulicz and Kümmel, on the other hand, have stated that the submaxillary and sublingual glands are more frequently infected than the parotid. The bacteria found in these cases were staphylococci, streptococci, diplococci, bacillus coli and oïdium albicans. Plewka notes that most of the cases showed evidence that the infection was ascending from the mouth, although the possibility of hematogenous source was mentioned in several. Lequeux described a case of staphylococcus infection of the gland in an infant whose mother was suffering from staphylococcus mastitis. Brandt observed an acute suppurative parotitis in a 7-day old child with gonorrheal infection of the umbilicus.

These infections in infants have been attributed to deficient function of the not yet fully developed salivary glands (Bretschneider) and to the acid or neutral reaction of the saliva (Mikulicz and Kümmel).

Battaglia (1927), after production of experimental trypanosomiasis, observed acute inflammation of the salivary glands, characterized by hyperemia, edema, leukocytic infiltration about the acini and ducts (chiefly round cell, eosinophilic and mast cell), degeneration of the epithelial elements and the finding of the trypanosome in the gland tissue. If the animal survived a chronic inflammation of the gland, productive in nature, resulted. In Madagascar, where trypanosomiasis is prevalent, this chronic inflammation is termed "mangy."

Heineke expressed doubt that diminution of salivary secretion by narcosis (ehloroform, morphin, etc.) predisposed to acute parotitis. However, many substances excreted through the salivary glands (iodin, bromin, mercury, lead, quinin, etc.) may lower the resistance of the gland and render it more liable to infection from the mouth. In support of this, Eichhorst has reported a case of parotitis following acute mercury poisoning in a woman, aged 24 years. The enlarged and inflamed parotid showed, on histologic study, a periductal infiltration with round cells and an intraductal inflammatory exudate. The glandular acini showed no change. This, he believed, bespoke stomatogenous infection. Aschoff, as well, observed paro-

titis following sublimate poisoning and expressed the view that the infection was probably ascending.

A primary pyogenic parotitis does occur in otherwise healthy individuals. Its incidence is perhaps more frequent than is generally recognized because it tends to run a mild course and subside spontaneously. Of 4 cases reported by Spurling and Stewart 3 recovered without operation. Direct extension of the infection along Stensen's duct to the gland is considered the most likely etiologic explanation.

**Discussion.** Since the experimental work of Rost it has been concluded by some that the anatomic picture of the gland in acute suppurative parotitis is quite the same whether the infection be hematogenous or ascending. Our own work has shown that the histopathologic findings are dissimilar in the two instances, that the hematogenous infection cannot be produced with the same facility as the ductogenous. The small ducts are involved early in the blood-borne infection, the large ducts late. On the other hand the findings in cases seen in *early stages*, viz., suppuration in and about the larger ducts alone, in more advanced cases the finer radicals involved as well, still later the inclusion of the acini in the infectious process all speak for the advance of infection through the ducts.

From the *bacteriologic standpoint* the failure to correlate the findings in the gland with those of the primary infection in most cases is strong evidence that the condition is not metastatic. Furthermore, the organisms commonly observed in acute parotitis are those that normally exist in an avirulent state in the mouth and in the lower part of Stensen's duct.

*Clinically* there occur a number of factors that favor the ascent of infection into the gland. In acute general infections and in the chronic debilitating conditions as well there occurs a lowering of the general body resistance and often a relative increase in virulence of the normal bacterial flora of the mucous surfaces. Diminution in the salivary flow that occurs during the febrile state and following dehydration due to excessive vomiting or purging is quite as important a predisposing factor. In surgical cases, too, the salivary secretion is decreased because of vomiting and restriction of fluids. Reflex cessation of salivary flow to a more or less complete degree accompanies laparotomy and visceral manipulation (Pawlow). The first stage of general anesthesia is accompanied by profuse salivation, but during the surgical stage the flow is absent and is very scant for some hours after operation. Pressure trauma to the gland itself during administration of anesthesia quite naturally lowers the resistance to infection; this, however, may apply quite as well to organisms circulating in the blood as to those present in the ducts.

There are, however, certain facts that point to the hematogenous mode of infection and cannot be overlooked. First may be noted

Rost's and our own experimental production of parotitis by injection of organisms into the nutrient artery. The fact that the parotid alone is involved in the vast majority of cases, the submaxillary and sublingual being quite unaffected, may well be construed as a predilection of the gland for organisms in the blood stream; this phenomenon is not uncommon in other tissues.

Post-operative parotitis occurs much more frequently when the operation has been carried out in a septic field and very often begins quite some days after the operation. Both of these observations have been considered favorable evidence of metastatic infection. The sudden onset with high fever and the high mortality have been thought to be more characteristic of sepsis than of local infection.

The 2 cases presented correspond anatomically to the descriptions of most of the earlier observers. Viewed from anatomic, bacteriologic and clinical standpoints, one might well believe that the infection in these glands was an ascending one.

**Conclusions.** 1. Acute suppurative parotitis occurs as a complicating and often terminal infection in a wide variety of conditions.

2. Most observers have considered the infection to be ductogenous in the vast majority of cases, though a frequent hematogenous origin is maintained by some.

3. Evidence in favor of each of these views has been presented.

4. Two cases of acute suppurative parotitis are reported in which the evidence favors ascending infection.

NOTE.—I am indebted to Prof. Dr. F. J. Lang and Dr. W. C. von Glahn for their invaluable assistance.

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## A CASE OF DIABETES MELLITUS AND FATTY DIARRHEA DUE TO CARCINOMA OF THE PANCREAS.

### TREATMENT WITH VERY HIGH CARBOHYDRATE DIET AND INSULIN.

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THE passage of fat and muscle fibers in the stools of patients with carcinoma of the pancreas is a frequent development of the disease. On the other hand, for the growth to progress far enough to produce diabetes is extremely rare. Warren,<sup>1</sup> though he states that carcinoma of the pancreas is of relatively more frequent occurrence in diabetics than in individuals in general, found no case of diabetes resulting from carcinoma in his recently reported series of 300 autopsied cases. In our patient the diabetes was unquestionably due to tumor encroachment. The carcinoma was slow-growing and relatively benign so that years of fairly comfortable living were allowed, and the patient was followed in the Massachusetts General Hospital for four years, from cholecystogastrostomy to death. During many months of this time he was carefully studied on the wards in an attempt to overcome the handicap of an insufficiency of both internal and external pancreatic secretions. So successful was this attempt, by a somewhat unusual method, that we feel the case worthy of report. We present it for what encouragement it may lend to the active treatment of a particularly distressing and hopeless form of malignant disease, as well as for what it may suggest or support in methods of diabetic treatment and in the management of pancreatogenous diarrhea.

**Report of Case.** S. M. (M. G. H. No. 273051), a white, married, Armenian shoetreeer, first entered the hospital on November 13, 1925, at the age of 46 years. He had been born in Turkey and had come to the United States at the age of 32 years. His past, marital and family histories were unimportant. The present illness had begun five years prior to entry, when the patient had had the first of five or six short attacks of right upper quadrant tenderness and moderately severe pain which had on one

occasion radiated to both scapulæ. The attacks had never been accompanied by nausea or vomiting, nor had the patient noted jaundice. He had had moderate diarrhea with some attacks, but otherwise he had always had a normal bowel movement regularly once or twice a day. Despite a good appetite he had lost 16 kg. during  $1\frac{1}{2}$  years preceding admission. Six weeks before entry he had begun to have intermittent generalized pruritus, especially of the feet, which had gradually grown worse, until finally he had come to the hospital for relief. Physical examination revealed only a weak, emaciated, jaundiced man with a moderately enlarged liver. He weighed 53.2 kg. The patient's chart and the routine examinations of urine, stools and blood were not remarkable. The icteric index was 20. The blood Wassermann test was negative. Roentgen examination of the gastrointestinal tract was negative, except for atony and sluggish peristalsis in the stomach. A Graham test by the oral method failed to show a shadow of the gall bladder.

Laparotomy was performed with a preoperative diagnosis of cholelithiasis, though the atypical history prompted a degree of uncertainty. The liver was found pale, smooth and extending a hand's breadth below the right costal margin. The spleen was normal in size. The gall bladder was distinctly enlarged and slightly thickened, and the common bile duct was dilated to the thickness of a thumb. No gall stone was palpable, but in the region of the head of the pancreas there was an irregular, moderately hard mass, about the size of an orange, frozen section from which showed chronic pancreatitis. An anastomosis was done between the gall bladder and the stomach. The patient made a good postoperative recovery and was discharged after 18 days symptom-free and relieved of his jaundice.

Detailed examination of the biopsy material showed a marked increase in connective tissue. The acini appeared normal and were collected in small lobules within the connective tissue. No islands were seen in the section examined. There was no suggestion of cancer.

Following discharge from the hospital the patient rapidly gained about 9 kg. After two months his liver was reported not palpable. He returned to work. His bowels moved from two to three times daily and seemed normal to him. He had no complaints excepting occasional sour stomach, gas and vague right upper quadrant distress while at work. Twelve months after discharge he developed chronic back strain, which eventually forced him to give up work. During the next  $1\frac{1}{2}$  years he lost 7 kg. He then suffered a brief attack of right upper quadrant pain which was dull, nonradiating and aggravated by any pressure under the right costal margin. An urinalysis showed 2 per cent sugar. The patient was sent to the outpatient diabetic clinic, where he was given a diet of approximately 107 gm. of carbohydrate, 68 gm. of protein and 177 gm. of fat. His urine quickly became sugar-free. However, he failed to gain and was, therefore, referred into the wards, which he entered on July 3, 1928,  $2\frac{1}{2}$  years after his previous entry.

At the time of admission he complained chiefly of itching for 3 weeks, exactly as before operation. The day before entry he had noticed jaundice. Physical examination revealed a markedly emaciated man who weighed 43.2 kg., or about 9 kg. less than he had at the time of his first entry. Jaundice was definitely present, and he showed, in addition, a rather deep, brownish pigmentation of the exposed parts of the skin. The spine was flexible and nontender. The liver dullness began at the sixth rib. Below the right costal margin was a large, somewhat irregular mass, extending downward 8 cm. in the nipple line, and thought to be a ptosed and enlarged liver. It was slightly tender to pressure. The spleen was not palpable. Other findings were sluggish tendon reflexes, dry and purplish skin over the feet, a blood pressure of 100 systolic and 66 diastolic.



Laboratory work revealed a red blood cell count of 5,000,000 per c.mm., a white blood cell count of 11,000 per c.mm. and a differential white cell count of neutrophils, 72 per cent; lymphocytes, 22 per cent; large mononuclears, 5 per cent; eosinophils, 1 per cent. The blood Hinton test was negative. Six morning urine specimens were normal. Five examinations each showed a small to medium-sized stool, soft, yellow to brown and negative for occult blood. No starch and only normal fat content were reported in three of the examinations. The icteric index was 20 at entry. A gastric analysis showed, fasting, a free acid of 33 cc.  $\frac{N}{10}$  HCl per 100 cc. of gastric contents, with a total acid of 45 cc. Forty minutes after an Ewald test meal the figures were 26 and 40 respectively. Bile was present abundantly in the material withdrawn. The guaiac test for occult blood was negative. Roentgen examination of the gastrointestinal tract was reported negative. Plates of the lumbar spine and pelvis were negative.

A month in the hospital and a diet as high as 2985 calories (carbohydrate, 250 gm; protein, 80 gm.; fat, 185 gm.) produced no gain in weight, though he was practically sugar free without insulin. The fasting blood sugar never rose above 104 mg. per 100 cc. The patient's itching did subside somewhat and the jaundice entirely disappeared soon after entry.

He continued the diet for six weeks at home, but was no better. He was, therefore, readmitted on September 14. At this time he complained of constant right upper-quadrant pain which was never severe enough to keep him awake, moderate upper thoracic back pain, mild itching of the feet, weakness and ravenous appetite without unusual thirst or polyuria. There was no new physical finding. The icteric index was 4. A sugar-tolerance test showed a rise, after 100 gm. of glucose by mouth, from 85 mg. fasting to 235 mg. at the end of the first hour and 332 mg. at the end of the second hour. Urinary sugar was absent at the end of the first hour, but was "4+" at the end of the second. The daily stool was now moderate in size, unformed, grayish-yellow, sour and showed microscopically many undigested muscle fibers, much of fatty acids, neutral fats and soaps and occasionally a little starch. A biopsy of skin from one of the heavily pigmented areas—the wrist—showed no hemosiderin. An analysis of the duodenal contents after the method of McClure, Wetmore and Reynolds<sup>2</sup> showed no lipase, practically no trypsin and abnormally low amylase. There was no pancreatic calculus demonstrable by a roentgenogram of the abdomen.

*Treatment and Course.* The patient was allowed to spend his time between bed and chair as he desired and nitrogen determinations on the stools and urine were begun. His subsequent stay of nearly 7 months was taken up with attempts by several means to improve his general condition. Chart I shows the curve of the patient's weight drawn against the amounts of food and insulin taken. The duration of certain other special measures are also indicated. He was started off on a theoretical maintenance diet, calculated from his weight and basal metabolic rate, and lost weight rapidly. The diet was, therefore, increased. During the next two months various attempts at artificial pancreatic digestion were made without consistent improvement either clinically or by changes in the amount of nitrogen in the stools and urine. (Table 1.) Pancreatin when given was administered  $\frac{1}{2}$  hour after meals, some of the time with and some of the time without alkali. The stools seemed to contain definitely less of muscle fibers and fatty elements during parts of this therapy, but there was no actual decrease in fecal nitrogen content.

During the period of experimentation on pancreatic preparation the dietary constituents were also changed a number of times without striking results, though when the carbohydrate had grown relatively high in the diet the patient began to gain a little weight. Carbohydrate seemed to

be the only one of the three food elements which was being adequately absorbed; so it was decided to test the effect of a material increase in its amount—especially of the simple sugars which might be better absorbed than the more complex forms. On November 24 the carbohydrate was, therefore, brought to a total of 500 gm. daily. Sixty-five per cent was in the form of sugar. Protein and fat were set at 100 gm. and 90 gm. respectively, and were kept constant throughout the remainder of the patient's hospital stay. Bowel movements increased to 2 or 3 a day, with the enlargement of the diet, but were otherwise unchanged. The dried weight of the stools per 24 hours, which had originally varied between 35 and 50 gm., increased to from 60 to 70 gm.

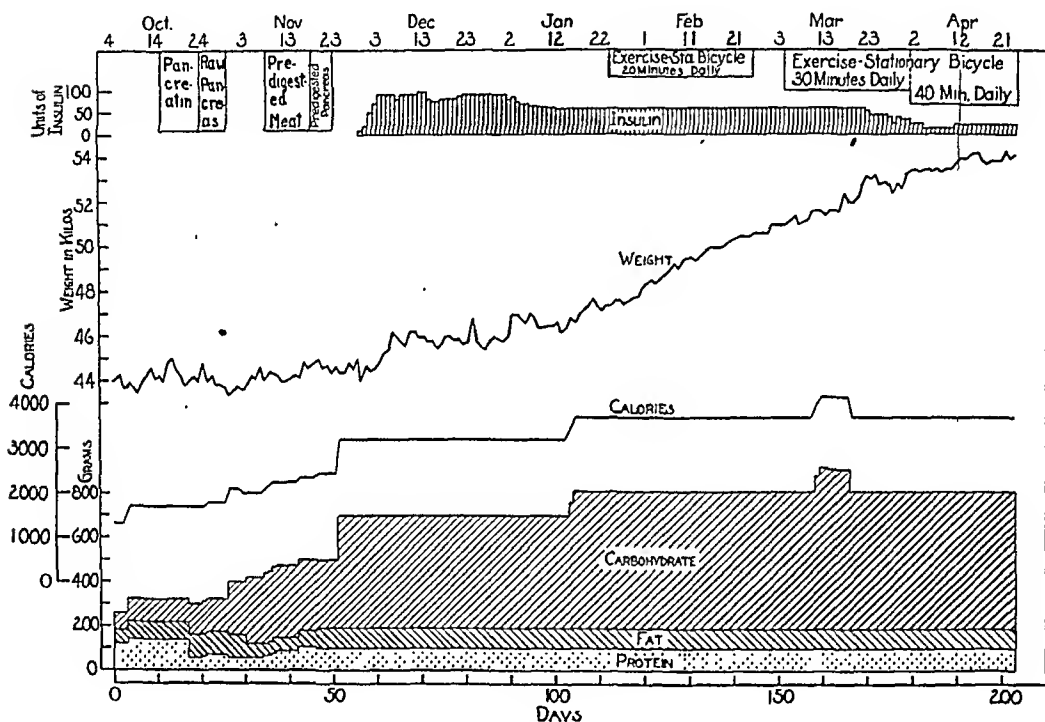


CHART I.—Course of patient's weight during treatment. The daily amounts ingested of carbohydrate, protein and fat are indicated along with the total calories. To allow for food unabsorbed the protein and fat values should probably be reduced by 25 per cent and the total calories by about 300.

With the increase of the carbohydrate content of the diet above 320 gm. the patient began to excrete large quantities of sugar in the urine, though the fasting blood sugar was always normal. He finally became sugar-free on 90 units of insulin a day, divided before meals in the amounts of 45 in the morning, 30 at noon and 15 at night. Food was given in three large main feedings, with several additional in-between feedings of carbohydrate alone. After a month insulin reactions resulted in a lowering of the dose to 40 units before breakfast, 12 before lunch and 7 before supper (59 daily). It may be seen that with the beginning of insulin and the high-carbohydrate intake consistent weight gain began.

On January 15, 500 gm. of banana were added to his daily diet. This increased carbohydrates to 120 gm. and raised the total calories to 3700. The per cent of monosaccharids and disaccharids constituted now between 75 and 80 of the carbohydrate intake. *This change produced no*

*glycosuria and the insulin dosage was left the same.* In 3 weeks the patient had gained 2.6 kg. more. The beginning of this consistent and rapid gain coincided with the addition of the banana in large amounts. A week or so later the patient was begun on graded exercise on a stationary bicycle. From this point on his appearance and general well-being improved steadily. His basal metabolic rate, previously -20 per cent, rose to normal.

TABLE 1.—NITROGEN INTAKE AND OUTPUT.

Days.	Average daily intake, gm.	Average daily output.			Balance, gm.
		Stools, gm.	Urine, gm.	Total, gm.	
Oct. 15 to Oct. 17 . .	22.4	1.6	16.1	17.7	+4.7
18 to 20 . .	22.4	3.4	19.2	22.6	-0.2
21 to 23 . .	9.6	1.5	9.5	11.0	-1.4
24 to 26 . .	10.5	1.5	7.6	9.1	+1.4
27 to 29 . .	10.9	1.2	10.1	11.3	-0.3
30 to Nov. 1 . .	9.6	1.4	7.0	8.4	+1.2
Nov. 2 to 4 . .	9.6	2.3	5.8	8.0	+1.6
5 to 7 . .	9.8	2.3	5.5	7.9	+1.9
8 to 10 . .	12.8	1.9	6.3	8.1	+4.7
11 to 13 . .	14.1	1.6	6.0	7.6	+6.5
14 to 16 . .	16.6	2.6	8.8	11.5	+5.1
17 to 19 . .	17.4	1.9	8.9	10.8	+6.6
20 to 22 . .	16.3	2.2	8.5	10.6	+5.7
23 to 25 . .	16.1	2.7	9.2	12.0	+4.2
26 to 28 . .	16.0	3.1	9.6	12.7	+3.3
29 to Dec. 1 . .	16.0	3.6	8.7	12.2	+3.8
Dec. 2 to 4 . .	16.0	3.3	8.4	11.7	+4.3
5 to 7 . .	16.2	3.0	7.4	10.5	+5.8
8 to 10 . .	16.0	2.8	7.8	10.5	+5.5
11 to 13 . .	16.0	2.0	8.1	10.1	+5.9
14 to 16 . .	16.0	3.1	7.7	10.8	+5.2
17 to 19 . .	16.0	2.8	10.6	13.5	+2.5
20 to 22 . .	16.0	2.3	9.0	11.3	+4.7
23 to 25 . .	16.0	2.1	6.6	8.7	+7.3
26 to 28 . .	16.0	3.0	8.0	10.0	+5.0
29 to 31 . .	16.0	6.1	8.0	14.1	+1.9
Jan. 1 to Jan. 3 . .	16.0	3.8	6.8	10.6	+5.4
4 to 6 . .	16.0	2.9	9.1	12.0	+4.0
7 to 12 . .	16.0	4.0	7.1	11.0	+5.0
13 to 18 . .	16.7	4.6	6.8	11.4	+5.3
19 to 24 . .	17.0	4.0	6.5	10.5	+6.6
25 to 30 . .	17.0	4.3	6.3	10.5	+6.5
31 to Feb. 3 . .	17.0	4.4	6.3	10.7	+6.3

In order to determine whether or not the gain on banana was anything more than a gain due to increased caloric intake, the banana was omitted and its calories replaced by the addition of sugar, mostly in the forms of honey and jelly. Under this régime the weight gain and insulin dosage remained unchanged.

On March 11 another 500 gm. of banana were added to the existing diet, which gave a total carbohydrate of 720 gm., of which 82 per cent was in the form of sugars. *This additional food also was followed by no glycosuria,* but was accompanied by a perhaps more rapid gain in weight. After a week its omission resulted in a series of insulin reactions which were not stopped by a reduction of dosage from 59 to 54 units, but which did stop

after a second drop to 48 units daily. This dosage was, however, further reduced, until at the end of 3 weeks the patient was receiving, without glycosuria, only 15 units a day, despite a diet of carbohydrate, 590 gm.; protein, 106 gm.; fat, 93 gm. Though the patient was sugar-free and gaining weight slowly on this régime, it was thought that progress was not as good as it had been when he was receiving more insulin; therefore, the dose was increased to 23 units daily, on which he was discharged, April 24, 1929. He was then taking an amount of insulin 67 units less than what he had required 5 months before, when his diet was 100 gm. poorer in carbohydrate.

At the time of discharge he weighed 54 kilograms, or 10 more than at entry 7 months before. He felt vastly stronger and complained much less of his right upper quadrant pain. There had been no recurrence of the thoracic back pain. The abnormal color of his skin had been replaced by a healthy tan. He had no itching. His blood pressure was 112 systolic and 80 diastolic. There was no demonstrable change in the size or consistency of the right upper quadrant mass.

He was passing daily two soft, copious, sour, grayish stools which showed microscopically much muscle fiber and fat and a little starch. Nitrogen in the stools showed during the high-caloric feedings a more elevated level than earlier in the patient's stay, despite a nearly unchanged protein intake. The loss was approximately 25 per cent. During a 6-day period on the final diet, the wet stool, weighed 2130 gm. and showed a fat content of 6.63 per cent. This represents a loss of 25.3 per cent of the fat intake for the period.

A blood-sugar curve following the ingestion of 100 gm. of glucose showed the following values after a fasting amount of 81 mg. per 100 cc.; at  $\frac{1}{2}$  hour, 123 mg.; at  $1\frac{1}{2}$  hours, 266 mg.; at 3 hours, 190 mg. There was no glycosuria during the test.

An estimation of the pancreatic ferments showed no change over the previous findings. In 1 cc. of duodenal contents there was no trace of lipolytic action. It developed a highest sugar of 0.16 mg. and a highest nonprotein nitrogen of 0.35 mg. According to Jones, Castle, Mulholland and Bailey,<sup>3</sup> in normal persons the lowest amounts developed by these ferments may be considered; for the lipolytic, 0.75 mg.; for the amolytic, 0.75 mg.; for the proteolytic, 1.5 mg.

The determinations were repeated on another day with no change in technique, excepting that 10 units of insulin were given  $\frac{1}{2}$  hour before the cream, so that when collection was begun the blood sugar was 50 mg. per 100 cc. There was no increase in the amounts of ferments present.

*Subsequent Course.* Seven weeks after discharge two sudden moderate hematemeses necessitated a 5 weeks' stay in the hospital. The bleeding stopped promptly, except as indicated by very slight amounts of occult blood in the stools, but the enforced stay in bed and curtailment in food resulted in a marked loss of strength and weight which he never completely recovered. Early in his stay he was placed on a strict milk and cream "gastric" diet, but large quantities of separated fat in the stools and the complaint of "sour stomach" necessitated a change to a carbohydrate diet and alkali, on which he was much more comfortable. There was no evidence of portal obstruction on physical examination. A Rosenthal liver-function test was normal. A gastrointestinal Roentgen ray study was negative except for a deformed, poorly visualized duodenum, due, it was thought, to adhesions. The gall bladder was seen to fill with barium and empty through the gastric stoma.

The patient remained easily fatigued, slightly anemic and gradually more distressed by right upper quadrant pain until 3 months later when the sudden onset of persistent vomiting again brought him to the hospital. The vomitus soon became watery, and black from changed blood. He

weakened rapidly. Four weeks after entry a sudden collapse followed by leukocytosis, slight fever and abdominal pain and distention led in 3 days to death. At no time, even at the very end, was there acetoneuria or glycosuria excepting the transient appearance of sugar in the urine after intravenous glucose administration. Insulin was used only in conjunction with these infusions.

The clinical diagnosis, which had been chronic pancreatitis with possible hepatic cirrhosis and bleeding esophageal varices, was, of course, poorly supported by the terminal events, in their suggestion of generalized peritonitis. However, no obvious explanation of the whole picture presented itself and, therefore, no new diagnosis was offered.

*Autopsy.* Save for marked emaciation, autopsy was negative excepting the abdomen. This showed, in the region of the head and the proximal portion of the body of the pancreas, a large, firm ovoid mass, roughly 15 by 15 by 11 cm. in size. The mass lay within the loop of the duodenum and behind the pyloric portion of the stomach which it displaced forward. On opening the duodenum it was found that the first and second portions were markedly dilated and that there were large areas on the posterior and medial aspects where the wall was being replaced by fungating, ulcerated masses of firm, translucent, mucoid, tumor tissue. Sections of the mass in various areas showed it composed throughout of the same tissue. The distal third of the pancreas was not involved by the tumor, but was distended, tense and fluctuant. On cross section it showed a large irregular cavity with ragged, grayish walls containing thick, turbid, grayish, purulent material. This space communicated by means of a small perforation with the abdominal cavity, and was presumably the source of a generalized peritonitis which appeared about 3 or 4 days old. The pancreatic ducts could not be identified. The common bile duct was found to enter the tumor behind the second portion of the duodenum, but it could not be followed further. Microscopically (Fig. 1) the tumor was divided by narrow fibrous septa into large alveolar areas filled with colloid material. In places these areas were lined by fairly well-differentiated, columnar, mucus-containing, epithelial cells, but in the greater part of the growth no epithelial cells were seen. Mitotic figures were rare. The body of the tumor showed no pancreatic tissue.

That portion of the pancreas which was not involved by the growth proper consisted of a shell of tissue, about 1 cm. in thickness and of a total outer measurement of 5 by 5 by 3 cm. It contained the abscess cavity described above. Microscopic sections showed an inner layer of granulation tissue with a marked acute and chronic inflammatory infiltration. In addition to a number of small abscess cavities, there were seen small areas of better differentiated tumor which grew apparently in dilated ducts and showed frequent mitosis, marked papillary formation and considerable colloid production. Finally, this shell-like portion of the pancreas showed numerous, well-preserved islands scattered through dense connective tissue (Figs. 2 and 3.) No acini were seen. The total amount of tissue containing islands was estimated to be not more than 5 per cent of the normal organ.

The liver was of average size and weighed 1330 gm. The surface was perfectly smooth and reddish-brown in color. The consistency was normal and the cut surface showed the usual markings. Microscopically there was slight fibrosis around the portal canals and fatty vacuolization of the central portions of the lobules.

The gall bladder was normal in size and thickness. There were many fine adhesions about the fundus near the operative stoma, which measured 0.6 cm. in diameter. Excepting for this anastomosis the stomach was normal.

No metastases were found. The anatomical diagnosis was: Colloid

adenocarcinoma of the pancreas, chronic interstitial pancreatitis, abscess of the pancreas, general peritonitis, ulceration of the duodenum, cholecystogastrostomy, adenoma of the adrenal.

**Comment.** This is an unusual clinical story and a rare type of lesion pathologically. Because of the rather benign course compared with that ordinarily encountered in carcinoma of the pancreas, the management of the case is of particular interest. Furthermore, in our present uncertainty of the exact pathology and pathologic physiology both in diabetes and in disturbances of fat absorption, the case is important because it offers two conditions rare in human beings: (1) diabetes obviously due to simple loss of pancreatic tissue; and (2) what from the autopsy findings, must have long been complete exclusion of the external secretion from the pancreas.

The patient's stools were typical of those associated with insufficiency of the external pancreatic secretion; grayish, bulky, mushy, sour, but of only slightly increased frequency. The fat loss was approximately 25 per cent of a daily 100-gram intake. Thaysen,<sup>4</sup> in 5 patients of his own with chronic pancreatitis receiving a similar amount of fat, and in 5 from the literature who received from 200 to 300 grams of fat daily, found a loss varying from 13 to 81 per cent and averaging about 50 per cent. He considers the loss of 10 per cent or more, of a 100-gram fat intake pathologic. Pratt<sup>5</sup> thinks that, in the absence of jaundice, and with sprue and tuberculosis of the intestines excluded, a loss of 40 per cent of fat is strong evidence of pancreatic insufficiency. In our case the percentage of fat in the stools would doubtless have been higher had the diet been richer in fat.

The nitrogen in the stools of our patient varied in daily amount from about  $1\frac{1}{2}$  grams at the beginning of the studies to 4 to  $4\frac{1}{2}$  grams at the end of four months. This represents a loss of from about 6 to about 25 per cent of the nitrogen intake (Table 1). Thaysen<sup>4</sup> found that his patients on a 100-gram protein intake (approximately 16 grams of nitrogen) lost from 8 to 50 per cent of the nitrogen, an average of 30 per cent. He considers a loss of over 3 grams of nitrogen abnormal. Pratt<sup>5</sup> found a loss of 14.5 to 60.6 per cent averaging 40 per cent in pancreatic obstruction.

As would be expected, the duodenal analysis showed the ferments much decreased. From the autopsy findings it is hard to ascribe even this small amount of ferment activity to the pancreas. In the duodenal analyses done by Thaysen<sup>4</sup> in cases of chronic pancreatitis, he found that the lipolytic activity was the most consistently low or absent and that the protein splitting function was the next most frequently diminished. Starch splitting was usually normal or slightly reduced. Our findings agreed.

In the matter of the treatment of external pancreatic insufficiency, our experience confirms the belief that the limitation of fat and protein and the administration of large amounts of carbohydrate

is the most satisfactory dietary procedure. For, in our case, as with most others reported, while there was marked loss of fat and nitrogen, there was very little starch to be found in the feces. This is, of course, not complete evidence that there was not carbohydrate loss, but, coupled with the weight response and the failure of other foods to absorb, it is considerable evidence that the carbohydrate was being well taken up. In the virtual absence of pancreatic amylase it is uncertain how the process was brought about. We had thought that perhaps the administration of much of the carbohydrate in the form of simple sugars may have helped, but Thaysen<sup>6</sup> reports a patient who thrived on a diet the main part of which consisted in thirty slices of bread a day, despite amylase which was low and frequently entirely absent in repeated duodenal analyses.

A second practical benefit from the diet is in its limiting of the fat intake, for high fat, with a resultant large amount passing through the bowel, undoubtedly increases the digestive disturbances, such as "sour stomach," fullness, and unrest, aggravates the diarrhea, and indirectly diminishes absorption of other elements. Its inadvisability was obvious in our patient when he was placed on the "gastric diet" of gruel and cream.

Protein apparently produces no such positive ill effects, but, in the absence of complete absorption, is as well not given in any larger amount than the approximate nitrogen requirement. It is notable that the patient here maintained a positive nitrogen balance throughout a 4-month period of observation. There was a rise of the stool nitrogens during the course of this period but the sum of these and the urine nitrogen virtually always remained well below the intake (Table 1).

Our attempts to benefit the patient by the use of pancreatic extract were as inconclusive as those of many other investigators.<sup>7,8,9</sup> However, because our patient maintained a positive nitrogen balance without any assistance, there was no practical need for attempting to augment his ferments so long as there was good absorption of carbohydrate. On the other hand, the alkali administered to our patient without pancreatic preparations definitely relieved certain vague digestive symptoms. In retrospect it is hard to say that these symptoms were not due to the carcinoma and were not relieved by the mechanism effective in the treatment of any ulcerated surface. On the other hand, we believe that on alkali therapy the stools were definitely smaller and more formed; in other words, his digestion was improved chemically. When we consider the rather narrow pH range in which intestinal ferments are active,<sup>10</sup> it is easily conceivable, in a patient whose stomach is secreting acid at an approximately normal level at the same time that the pancreatic secretions are markedly below normal, that the administration of alkali an hour or two after meals might well augment the digestion in the upper bowel.

We failed in a rather crude experiment wherein we attempted to demonstrate increase in the output of the external pancreatic secretion following the administration of insulin, as has been shown to occur in normal men and animals.<sup>11,12</sup> A sufficient reason was apparent at autopsy. There was in all probability no glandular tissue present to be stimulated.

The patient was obviously a very mild diabetic despite even the marked final reduction in number of the islands of Langerhans. There were no polyuria, polydipsia, or other symptoms which could be directly attributed to the diabetes. His fasting blood sugar was always normal, as was the morning urine. He was comparable to Thaysen's<sup>6</sup> patient with chronic pancreatitis whose pancreas at autopsy weighed only 25 grams and contained only a few islands in the tail, but who was, nevertheless, but a mild diabetic. This marked discrepancy between the amount of glandular tissue and the degree of diabetes seems to be the rule. Labbé's case<sup>13</sup> of a huge cyst of the pancreas, which involved all but a very small amount of tissue in the head, showed neither diabetes nor clinical evidence of lack of internal secretion. In marked contrast is Joslin's Case No. 896,<sup>14</sup> a true diabetic in whom cancer of the pancreas developed some years after the onset of diabetes. There was a similar extensive involvement of all but the tail, but a very dissimilar, extremely severe, terminal diabetes.

The patient's natural tolerance for carbohydrate was striking. Without insulin he remained sugar-free on a diet of carbohydrate 320 grams, protein 102 grams, and fat 89 grams; or an estimated available carbohydrate of 371 grams (when 25 per cent of fat and protein is considered lost in the stools). He might have been able to take an even greater amount successfully, but, though no attempt was made to estimate it accurately, we feel that this diet was near his limit. Several unusual factors undoubtedly had a part in the production of this rather high tolerance. With the large percentage of fruit sugars in the food, levulose was doubtless more plentiful than in the ordinary diet. The absorption from the intestines was possibly slower than in the ordinary diabetic. There was probably a diminished diurnal curve in the blood sugar such as Geyelin<sup>15</sup> has found in patient on high-carbohydrate-low-fat diets. Finally a loss of carbohydrate in the stools may have made the actual intake less than it appeared.

Perhaps more interesting than the patient's natural tolerance were the variations in the insulin-carbohydrate ratio which developed during his hospital stay. Porges and Adlersberg,<sup>16</sup> Sansum,<sup>17</sup> Geyelin and Mackie,<sup>18</sup> and others have noted a very appreciable fall in the insulin requirements of their diabetics taking high-carbohydrate diets. Our patient's insulin requirement fell markedly during his sustained high-carbohydrate diet; though exercise and increase in strength and well-being also undoubtedly improved him,



too, in the manner so well illustrated by Root's case,<sup>19</sup> where the insulin requirement of a long bed-ridden patient fell, during graded passive and active exercise over 14 weeks, from 101 to 18 units per day, despite little change in diet. (His patient's diet was moderately low in carbohydrate and high in fat.)

Much more unusual to us, however, was our patient's seemingly remarkable ability to accept sudden, large increases in carbohydrate intake without resultant glycosuria despite no change in the insulin dosage. MacLeod<sup>20</sup> has described how, in depancreatized dogs, there is rapidly augmented efficiency of insulin per unit as the proportion of glucose to insulin is increased. Thus, with our patient's high-carbohydrate intake and relatively low-insulin dosage, increases in carbohydrate which were actually large became comparatively less and less. But more important than this is a phenomenon described by Porges and Adlersberg,<sup>16</sup> who found that their patients, after periods on high-carbohydrate-low-fat diets, developed elevated renal thresholds for sugar. Thus, our patient on his second sugar tolerance test lost no sugar in the urine despite a blood sugar as high as 266 milligrams. Apparently by being able to maintain a higher blood-sugar level without glycosuria, he was able to start at insulin-carbohydrate ratios bordering on the production of hypoglycemic reactions, as on January 13 and on March 27, and either increase markedly his carbohydrate, or substantially decrease his insulin, without the loss of sugar in the urine. This wide margin of safety is offered by Porges and Adlersberg<sup>16</sup> as one of the advantages of high-carbohydrate diets; a fact also appreciated by Geyelin<sup>15</sup> who has remarked that there is a decreased frequency of insulin reactions in his patients on similar diets.

Porges and Adlersberg<sup>16</sup> found in their patients both with and without insulin that there were definitely improved sugar-tolerance curves after periods on high-carbohydrate-low-fat diets, over what there had been following low-carbohydrate-high-fat feedings. Similar tests on our patient at the beginning and end of his hospital stay did not show this change definitely, probably because his impaired fat absorption, as well as his constantly rather low-fat diet, kept him from being at any time on a high-fat intake comparable to that of Porges and Adlersberg's patients. For it seems logical to suppose that the difference in glucose tolerance curves after high-fat and high-carbohydrate diets is more due, as Geyelin<sup>15</sup> believes, to a deleterious effect of high fat than to any benefit inherent in high carbohydrate *per se*.

With the present uncertainty as to the mechanism in the production of diabetes, it would be of particular interest if, in this case with a simple marked loss of pancreatic tissue, we could distinguish any clinical differences from the usual type of diabetes, especially that in the younger person. The disease in our patient obviously differs from the juvenile type in its clinical mildness, but beyond



FIG. 1.—Tumor, showing at right the small number of cells and large amount of mucin which was typical of its major portion.  $\times 35$ .

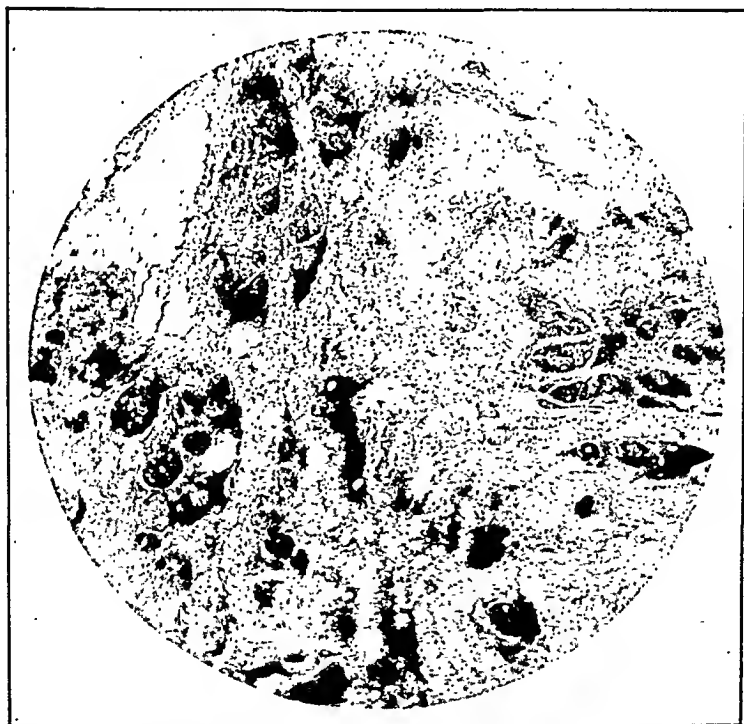


FIG. 2.—Tail of pancreas, showing persisting islands scattered through scar tissue which has completely replaced the acini.  $\times 35$ .

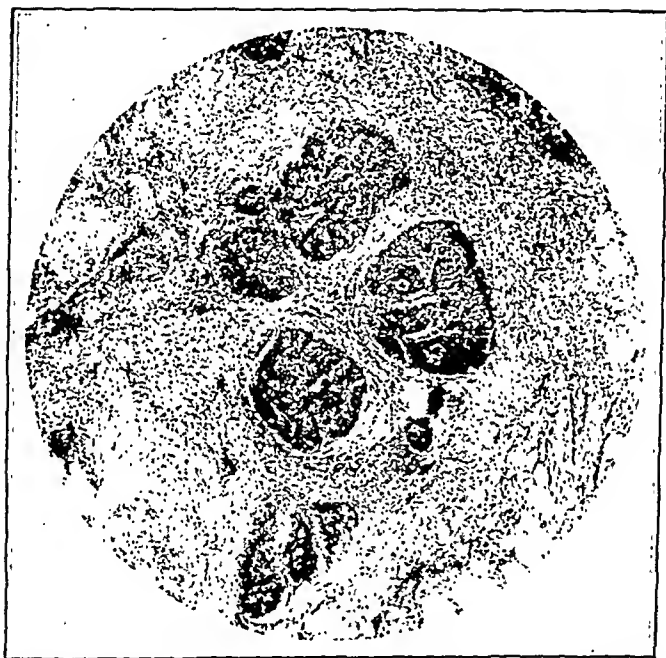


FIG. 3.—Tail of pancreas, showing higher power view of island remnants.  $\times 45$ .

this we have detected no variation. His reactions to diet have been strikingly similar in character to those of ordinary diabetics fed by Rabinowitch<sup>21</sup> diets high in carbohydrate and low in fat and protein.

Insulin appears to have been invaluable in our treatment of this patient in that it made possible the necessary large food intake. However, we believe that it contributed very definitely to the gain in weight and strength by another as yet mysterious mechanism, which doubtless functions also in the insulin treatment of undernourished nondiabetics. It may be seen that the patient's weight curve tends definitely to flatten out toward the end of the chart, coincident with the reduction of the dose of insulin. Of course, it might be assumed that the 40 minutes of bicycle riding which he was finally doing were exceeding his optimum for exercise, and were actually detracting from the weight increase; or that the carcinoma or a decreased absorption was responsible. But the leveling of the weight curve is too abrupt and coincides too closely with the marked reduction in the insulin dosage to seem mainly due to anything else. The reduced rate of gain must have been due to the reduced insulin dosage, and, since there was no sugar in the urine and no reduction in the food eaten, we must further assume that the action of insulin in stimulating weight gain was something more than either a simple prevention of loss of sugar, or a stimulation of appetite.

The effect of exercise on the patient cannot be definitely determined from our data but it was our distinct clinical impression that the increase in weight, along with improvements in the metabolism and general well-being, was very favorably influenced by the bicycle riding.

It is interesting to speculate, in this case, upon the probable duration of the carcinomatous involvement of the pancreas. We feel that the mass found at operation 4 years before death probably contained cancer which failed to be revealed by the small bit of tissue removed for examination. The symptoms during most of the 5 years preceding must surely have been due to pancreatitis.

Our case would seem to illustrate the value of cholecystogastrostomy as a procedure in conditions producing permanent obstruction of the common bile duct. The microscopic examination of the liver showed evidence of mild liver infection, probably much like that observed by Gatewood and Lawton<sup>22</sup> in their dogs with cholecystogastrostomy. Clinically, there was also evidence of such involvement at the time of the second admission, when there was an icteric index of 20 despite plenty of bile in the gastric contents. The jaundice came on during a period of low-carbohydrate-high-fat diet given because of the glycosuria and cleared up rapidly during the more favorable higher-carbohydrate intake.

The pigmentation, which was noted early in the patient's stay

in the hospital and which cleared definitely with his improvement and the coming of winter, seems to have been like that noted by Thaysen<sup>4</sup> in one of his cases of chronic pancreatitis. He quotes Adler as reporting in similar cases a color like that in bronzed diabetes.

**Summary and Conclusion.** We have reported a case of colloid adenocarcinoma of the pancreas of probably 4 years and possibly longer duration. During the last 4 years of his life the patient tolerated well a cholecystogastrostomy done to relieve biliary obstruction. During the last year and a half, he was known to have mild diabetes, and during the last year he exhibited the classic picture of external pancreatic insufficiency.

The emaciation and general debility produced by all three of these factors, carcinoma, pancreatogenous fatty diarrhea, and diabetes, were extremely well combated by treatment with a very high-carbohydrate diet plus insulin. Adequate digestion and absorption from the intestine were maintained, the utilization of carbohydrate foods was vastly improved, and there was a marked resultant increase in weight and strength. The general effects of the carcinoma were successfully resisted, although its pain, never severe, persisted and hemorrhage and infection secondary to the tumor finally led to rapid death.

From this case we are able to conclude, in agreement with other observers, that a high-carbohydrate intake is by far the most advantageous type of diet in external pancreatic insufficiency. Enzyme preparations, if not valueless, may be entirely unnecessary. The use of insulin is to be recommended not only for its aid in the prevention of glycosuria, but also for what general metabolic effect it has in the production of weight increase. High-carbohydrate-low-fat diet with insulin enhances rather than impairs carbohydrate tolerance.

We have been unable to demonstrate that diabetes produced by encroachment of tumor tissue on the pancreas differs clinically in any other way than in degree from so-called "true" diabetes.

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## JERUSALEM ARTICHOKES AND LIVER IN THE TREATMENT OF DIABETES MELLITUS.

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THE search for a carbohydrate more utilizable than dextrose by the diabetic patient, and for a foodstuff of therapeutic value in this condition, dates back to the nineteenth century. The addition of insulin to our armamentarium, bringing with it an even greater need than heretofore for strict dietary control, has not obviated the desirability of such foodstuffs. The following is a report of the experimental trial of two such materials, recently advocated for the treatment of diabetes mellitus.

**Jerusalem Artichoke.** The tubers of the Jerusalem artichoke (*Helianthus tuberosus*) contain, according to a recent analysis,<sup>1</sup> inulin, inulin-like substances and a significant amount of sucrose. The preparation and digestion of the artichokes probably result in the formation of a considerable proportion of levulose in the intestinal tract.

Joslin<sup>2</sup> and Root and Baker<sup>3</sup> have recently reported favorable results from the use of Jerusalem artichokes in the treatment of diabetes. The latter authors, whose paper contains an excellent

bibliography of previous work in this field, observed the effects of the ingestion of a single portion of prepared artichokes by normal and diabetic subjects. Basing their judgments chiefly on changes in the respiratory quotient and heat production, they concluded that the carbohydrates in Jerusalem artichokes are utilized by the diabetic, the results being quite similar to those obtained with levulose. Their clinical observations, however, are apparently based on favorable reports from patients using artichokes in their diets at home. These patients are reported to have been able to eat moderate amounts of artichoke without increasing glycosuria when this was present, and without producing glycosuria when it was previously absent. Some patients using artichokes were able to add other foods so as to increase their total caloric intake by 11 per cent, although the insulin dosage was increased by only 3 units. More recently, Carpenter and Root<sup>4</sup> have reported a more carefully controlled clinical experiment on a diabetic patient, taking one-half of his carbohydrate intake in the form of Jerusalem artichokes, while in the hospital for 6 days. From analyses of the food intakes and the feces, and from studies of the respiratory exchange and the composition of the blood and urine, these workers concluded that Jerusalem artichokes furnish carbohydrates which can be absorbed and utilized by a patient with diabetes mellitus.

A closer examination of the results of the above-mentioned work and a consideration of other work of a contradictory nature leave some room for doubt as to the validity of the conclusions drawn. Thus in summarizing his discussion of levulose, inulin and Jerusalem artichokes Joslin (p. 631) says: "Levulose seems to cause a different type of metabolism from dextrose, possibly due to the conversion of levulose in part into fat by the diabetic or to a more active stimulation of insulin production. Similarly inulin and lower polymers of levulose in the form of Jerusalem artichokes have been used by our patients with pleasure and benefit."

Granting for the moment, that the substances in question may act in the manner suggested by Joslin, one might question the desirability of such effects in the diabetic. The administration of these substances as a source of fat is, to say the least, unnecessary, while the disastrous result of the carbohydrate spree has been frequently used as an argument that stimulation of the insulin production mechanism of the diabetic pancreas is undesirable. Root and Baker<sup>3</sup> observed undoubted increases in the respiratory quotient and heat production of diabetics after ingestion of Jerusalem artichokes and levulose, although their results with inulin were hardly significant. But, aside from the fact that it is difficult to accept the use of the respiratory quotient and heat production as a reliable criterion of carbohydrate utilization in diabetes,<sup>5</sup> they have failed to report the effects of comparable amounts of dextrose on the same patients under the same conditions. Such a control

has been reported by Carpenter and Root,<sup>4</sup> who substituted baked potatoes for Jerusalem artichokes on one day of their patient's stay in the hospital. Although the patient showed a rise in glycosuria and the blood sugar level on the day in which potatoes were the source of carbohydrate, he derived, according to their calculations, just as great a proportion of his caloric requirement from carbohydrate as on the days of artichoke feeding. Their results, therefore, can hardly be held to prove that Jerusalem artichokes furnish the diabetic a more available form of carbohydrate.

All the above-mentioned investigations, including our own, are subject to the general criticism that it is impossible to tell, at any given time, how much insulin is being secreted by the pancreas of a particular subject. This does not apply to the work of Campbell and Markowitz,<sup>6</sup> who used completely depancreatized dogs kept in a constant known state of partial diabetes by the injection of insulin. From a comparison of the effects of levulose and inulin with the effects of equivalent amounts of dextrose on such animals, these workers concluded that there was no evidence that greater quantities of the former substances can be utilized by the diabetic organism than of glucose itself. In the clinical realm Wescott and Wise<sup>7</sup> have recently reported the failure of a diabetic patient to utilize dried artichoke powder.

*Method.* The observations reported by us were made on diabetic patients in the Michael Reese Hospital, receiving carefully controlled diets, with or without insulin. All food materials were weighed, their composition and caloric value being calculated from standard tables. As a preliminary to each experiment, the diet was gradually increased until the patient showed little or no further increase in tolerance and was excreting a small amount of sugar in the urine. Jerusalem artichokes were then substituted in the diet so that the patient was receiving a considerable proportion (more than 50 per cent) of his carbohydrate intake in this form, while the distribution of calories between protein, fat and carbohydrate remained as before. The only essential change made was, therefore, in the source of part of the carbohydrate intake.

The results were judged by the total daily excretion of glucose and nitrogen in the urine. These were determined by the Somogyi modification of the Shaffer-Hartmann method and the method of Kjeldahl respectively. The determination of temporary fluctuations in gaseous metabolism or blood chemistry was not attempted. We are indebted to the Pabst Dictary Products, Inc., for the Jerusalem artichokes used in this work, and for financial assistance. The artichokes were supplied in the form of flakes similar to potato chips, dried fresh slices and a purée. Current analyses of these products were furnished and used by us. Our observations are recorded in tabular form on page 678.



TABLE 1.—JERUSALEM ARTICHOKEs.

Case.	Period.	Gm. carbo. in artichokes.	Diet.				Insulin daily.	Excretion in urine.			Remarks.
			Composition.			Cala. per kg.		No. of days.	Average N.	Average G.	
			P.	F.	C.						
1. (M. L.)	Preliminary	..	70	140	70	29	0	6	11.6	0.73	Experiment discontinued because of weight loss, onset of irregular periodic fever associated with moisture in lungs of phthisical nature.
	Preliminary	..	75	150	75	31	0	2	10.3	2.24	
	Preliminary	..	75	150	90	32	0	7	12.0	5.37	
	Control	..	75	150	100	33	0	12	12.6	13.73	
	Artichoko	20	75	150	100	33	0	6	10.9	20.46	
2. (A. F.)	Artichoko	40	75	150	100	33	0	5	9.8	19.03	
	Artichoko	60	75	150	100	33	0	5	8.8	16.66	
	Preliminary	..	60	150	50	24	20	5	10.4	1.39	
	Preliminary	..	60	150	60	25	20	2	8.9	0	
	Preliminary	..	65	150	70	26	16	8	10.5	2.91	
3. (A. R.)	Control	..	65	150	85	27	16	10	11.7	22.51	
	Artichoko	47	65	150	85	27	16	8	13.1	38.08	
	Preliminary	..	55	130	65	31	0	5	8.0	2.35	
	Preliminary	..	55	135	85	33	0	4	10.8	5.46	
	Preliminary	..	55	135	100	34	0	4	8.5	5.44	
4. (A. S.)	Preliminary	..	55	140	115	36	0	6	8.0	9.42	
	Control	..	55	145	135	38	0	12	7.5	7.51	
	Artichoko	30	55	145	135	38	0	8	6.4	7.24	
	Artichoko	26	50	125	50	17	0	2	7.2	0.05	
	Artichoko	32	55	130	60	18	0	5	6.9	0.35	
5. (A. K.)	Artichoko	44	60	130	75	19	0	7	7.3	0.19	
	Control	..	60	130	75	19	0	10	7.7	0.18	
	Preliminary	..	60	160	80	35	10	12	9.9	13.02	
	Preliminary	..	60	165	100	37	10	10	11.1	13.76	
	Control	..	60	165	120	39	10	9	11.2	16.65	
	Artichoko	70	60	165	120	39	10	8	8.4	0.97	
	Control	..	60	165	120	39	10	18	7.6	6.41	
	Artichoko	68	60	165	120	39	10	9	8.4	2.65	
	Control	..	60	165	120	39	10	10	7.7	18.43	
	Artichoko	68	60	165	120	39	10	16	7.6	2.58	
	Control	..	60	165	120	39	10	6	10.3	4.68	
Total reducing substance per 100 gm. stool: Control, 4.37; control, 4.18; artichoko, 3.33; artichoko, 3.65; experiment complicated by purulent infection of toes.											

**Discussion.** The results of Experiments 1 to 4 are quite negative and yield no evidence that Jerusalem artichokes are of any value in the treatment of diabetes mellitus. The nitrogen excretion remained fairly constant throughout each experiment, while the sugar excretion either remained the same or increased somewhat when artichokes were substituted in the diet. In Experiment 5 the sugar excretion was consistently lower during the periods of artichoke feeding than during the control periods. This may mean that some cases of diabetes mellitus differ from others in that they are benefited by the use of Jerusalem artichokes. A consideration of the control periods of this experiment, however, reveals so great a variation in tolerance to the usual forms of carbohydrate that conclusions as to the beneficial rôle of artichokes would be quite unwarranted. The determination of the total reducing substances in the stool of this patient, before and after artichoke feeding, would seem to indicate no lack of absorption of the artichokes from the intestinal tract. The results of this experiment may depend on the complicating infection noted.

In any case, since the above results are not uniformly and completely negative, and especially because of the small number of cases investigated, it cannot be held that these experiments prove that Jerusalem artichokes are of no value in the treatment of diabetes mellitus. It seems fair, however, to conclude that these few but carefully controlled experiments yield no evidence that artichokes are of any value in this condition. In view, therefore, of the contradictory nature of some of the previous work in this field and in view of the criticisms which have been raised by the authors, the rational use of Jerusalem artichokes as a therapeutic agent must await further experimental support.

The remarkable increase in tolerance of all our patients as their caloric intake was increased, at the beginning of each experiment, is worthy of note. We have observed this phenomenon clinically in many patients in the hospital, even where we had reason to believe that they followed their dietary prescriptions most carefully at home. Whether due to the greater exactness of treatment or to the freedom from routine cares, it emphasizes the importance of using adequate control periods in work of this kind. It probably also explains the positive results obtained by others on patients observed for short periods in the hospital, and the favorable reports from patients treating themselves with renewed vigor at home, under the stimulating influence of a new dietary régime.

**Liver.** References to the use of liver for the treatment of diabetes mellitus may be found in the older French medical literature. More recently, on this continent, Blotner and Murphy<sup>8,9</sup> have reported the favorable influence of the ingestion of liver or certain liver fractions, on the blood sugar level of diabetic patients. According to these workers, 180 gm. of liver has an effect on the

TABLE 2.—LIVER.

Case.	Period.	Liver, gm.	Diet.				Insulin daily.	Excretion in urine.		Remarks.
			Composition.			Cals. per kg.		No. of days.	Average G.	
			P.	F.	C.					
1. (M. L.)	Control	...	75	150	75	36	0	3	12.1	During the 10 days of this liver feeding period, 84 gm. additional glucose was given to treat insu- lin reactions.
	Liver	180	75	150	75	36	0	8	25.5	
2. (J. F.)	Control	...	75	150	75	36	0	3	14.6	
	Liver	180	70	150	80	33	15	5	56.9	
3. (W. G.)	Control	...	70	150	80	33	15	5	60.3	
	Liver	180	50	125	40	34	60	5	14.9	
4. (S. K.)	Control	...	50	125	40	34	60	4	11.6	
	Liver	180	70	140	50	40	60	11	12.9	
5. (I. A.)	Control	...	70	140	50	40	60	10	12.7	
	Liver	180	70	125	100	31	60	5	11.5	
6. (S. K.)	Control	...	70	125	100	31	60	4	23.4	
	Liver	180	70	125	100	31	60	5	0	
7. (I. A.)	Control	...	70	125	100	31	20	5	19.2	
	Liver	180	70	125	100	31	20	3	28.8	
8. (I. A.)	Control	...	70	160	70	36	0	6	19.8	
	Liver	180	70	160	70	36	0	6	26.8	
9. (I. A.)	Control	...	70	160	70	36	0	2	33.9	

blood sugar equal to that of from 10 to 15 units of insulin. They conclude that "liver contains a blood sugar reducing substance active when taken by mouth, nontoxic and with an effect on the blood sugar concentration similar to that obtained with insulin."

Using normal and depancreatized dogs, DePencier, Soskin and Best<sup>10</sup> obtained no evidence that the ingestion of fresh raw liver lowered the blood sugar or sugar excretion of these animals. The data presented below are the results of a therapeutic trial of fresh liver on cases of human diabetes mellitus. The experimental method was similar to that described for Jerusalem artichokes. The amount of liver substituted in the diet was 180 gm. to conform with the amount used by Blotner and Murphy. The figures given by these authors for the composition of calf's liver were also used as a basis for calculation.

**Discussion.** The results of these experiments are largely negative. Although one liver period in Experiment 3 showed hypoglycemic reactions which might be taken as evidence of a blood sugar reducing effect, and another liver period in Experiment 4 showed a lack of glycosuria previously present, the other liver periods in these experiments yielded glycosuria figures which negate any conclusions which might be drawn as to the favorable influence of liver in these cases. As was pointed out above, it has been reported that liver does not lower the blood sugar level of normal or depancreatized dogs.<sup>10</sup> Moreover, Bowen,<sup>11</sup> when feeding liver in a case of combined diabetes and pernicious anemia, found no evidence of a blood sugar lowering effect or of improvement of the diabetes. But whether the ingestion of liver does or does not cause a temporary reduction in the blood sugar of humans suffering from diabetes mellitus, it seems clear that it has little if any therapeutic value in this condition as judged by the urinary sugar excretion.

These experiments were carried out prior to those with artichokes and are subject to the criticism mentioned above, that of using control periods which are too short. Since this, however, would tend to render the results falsely positive instead of negative, and since control periods were observed both before and after liver feeding, this defect cannot be held to invalidate the results in this instance.

**Conclusion.** These experiments yield no evidence that Jerusalem artichokes or liver are of any appreciable therapeutic value in the treatment of diabetes mellitus.

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## THE RÔLE OF THE STREPTOCOCCUS IN ARTHRITIS DEFORMANS.

(AN IMPROVED CULTURAL METHOD).\*

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THE recent bacteriologic studies of rheumatoid arthritis or arthritis deformans indicate that it is due to a streptococcus infection. An Alpha type streptococcus has been isolated in a high percentage of cultures from the blood, joint fluid and primary foci. The same organism has been found in joint tissues. Typical lesions have been produced by inoculating animals with this streptococcus. The results obtained from specific vaccine therapy also suggest that this arthropathy is caused by a streptococcus of the Alpha type.

Before further discussion of the bacteriology of arthritis deformans, certain other factors should be mentioned. Some families appear to have an arthritic tendency and certain types of individuals are particularly susceptible to arthritis. Trauma is a factor in producing lowered resistance in a joint, as shown not only in patients but also by animal experiments. Fatigue, especially long continued fatigue and particularly when combined with exposure to cold and wet, is an especially important factor. Focal infection and even

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bacteremia are frequently present without the development of arthritis. If, however, the resistance is lowered through fatigue or exposure the conditions become ideal for localization of such an infection in the joints. Pemberton<sup>1</sup> showed that a high percentage of soldiers who developed rheumatoid arthritis gave a history of standing in water, marching or sleeping in the rain, or long exposure to cold weather.

The fact that chronic deforming arthritis is practically limited to the north temperate zone and is most prevalent along the Atlantic seaboard and around the Great Lakes indicates that there is a climatic factor. The prevalence of upper respiratory infections in this climate will account for a high percentage of subsequent joint infections. Sudden changes in temperature and barometric conditions play parts in joint physiology and pathology which are but little understood. Not only equable but also dry climates are considered ideal for "rheumatic" individuals.

It has long been recognized that the predisposing factors above mentioned played important parts in the actual onset of symptoms, but because of the characteristics of the disease an infectious exciting cause was suggested by many observers. Nearly 20 years ago Billings<sup>2</sup> called attention to focal infections and their etiologic relations to arthritis. In 1924 Rosenow<sup>3</sup> cultured enlarged lymph nodes from patients with chronic infectious arthritis and was able to isolate the *Streptococcus viridans* in several instances. Moon and Edwards,<sup>4</sup> in 1917, reported nonhemolytic streptococcus from the blood cultures in about 20 per cent of 83 arthritis cases. Richards,<sup>5</sup> in 1920, claimed 15 positive blood cultures in a series of 104 cases and 4 positive joint cultures in 54 cases. Hadjopoulos and Burbank<sup>6</sup> took cultures from the blood in 145 cases of chronic arthritis and obtained a streptococcus in 15 (10 per cent). Forkner, Shands and Poston,<sup>7</sup> in 1928, cultured streptococci from joints from 16 per cent of 63 cases. A great majority of the investigators look on the streptococcus as the bacterial agent responsible for the disease, but some believe that the staphylococcus, the gonococcus, the diphtheroid bacillus or some other organisms, as well as the streptococcus, may produce arthritis deformans.

The extensive work of Cecil, Nichols and Stainsby,<sup>8</sup> in 1929, deserves special attention. They reported blood cultures on 154 cases of chronic infectious arthritis with 96 (62.3 per cent) positive for a short-chained streptococcus. In 33 of 49 cases joint cultures were positive for the same organism. Control blood cultures were made on 104 cases and control joint cultures on 18 cases, all of which were sterile. They used a special culture technique which consisted in removing inhibitory substances from the patient's blood by separating the serum from the clot and culturing the clot in specially prepared heart infusion media. The cultures were incubated for several weeks and subcultured from time to time. Through cul-

tural studies, including fermentation, agglutination and absorption tests, they established the identity of the streptococcus isolated from the blood, joint and primary foci of arthritic patients. They also produced typical deforming arthritis in the joints of rabbits by inoculating them with the "typical" strain of streptococcus isolated from the patient's blood, and the organism recovered from the blood of the rabbits was found through cross agglutination to be the same as the original organism.

A modification of Cecil's method was reported by Gray and Gowen<sup>9</sup> in January, 1931. This preliminary report was based on the bacteriologic studies of 37 cases of arthritis deformans and 32 control cases. Blood and joint cultures were positive for Alpha type streptococcus in 25 (67.6 per cent) of the arthritic patients. But more important than the high percentage of positive cultures was the fact that they were obtained after a very short incubation period, *i.e.*, after 1 to 4 days. Cecil's positives appeared after an average of 17 days and some required 30 days' incubation. His cultures were subcultured frequently, while ours were not opened until a clouding of the media appeared. It is of great significance that this organism, which had heretofore been so sluggish in primary cultures, could be grown so quickly. This modified method presents three distinct advantages: (1) A saving of time and labor, (2) elimination of a source of contamination, (3) and most important, it makes possible the development of an autogenous vaccine in a minimum length of time.

The improved cultural method consisted of enriching Cecil's medium with glucose, adding gelatin to create oxygen tension and using calcium carbonate as a buffer. This method in detail is as follows:

The patient's arm is prepared by two coats of iodine, washed off with alcohol and 20 cc. of blood is drawn from a vein in the arm and placed in two sterile dry test tubes (10 cc. in each). These are placed in the ice box over night. The serum is removed, clot broken up, and the pieces of clot placed in each of two 100-cc. bottles containing 50 cc. of media. The media is prepared as follows: Fresh beef heart is freed from fat and fibers, ground finely in a meat chopper and infused at ice box temperature over night, using 500 gm. ground meat and 500 cc. tap water. The next morning the infusion is warmed to 20° to 25 C.° and squeezed through a flannel bag. The filtrate is then boiled slowly for 1 hour and filtered through paper. It is then made up to volume, 1.5 per cent peptone (Witte), 0.5 per cent chlorid of sodium, 1 per cent dextrose, and 1 per cent gelatin added. This is then placed in the Arnold sterilizer for 20 to 25 minutes to dissolve the ingredients. It is then titrated to pH 8 and placed in the Arnold sterilizer for 1 hour. It is filtered through paper and retitrated. If the pH has dropped below 7.8 it should be retitrated to that figure. It should not be below a pH of 7.8 before placing in bottles. The bottles are prepared beforehand by placing about a teaspoonful of calcium carbonate (*c.p.*, powdered) in each of them, plugging with cotton, or cheese cloth and cotton, and sterilizing in the dry sterilizer for 1 hour. In these sterile bottles 50 cc. of

medium are placed and sterilized in the Arnold sterilizer for 30 minutes on 3 successive days. At the end of 3 days it is titrated and if the pH is 7.6 to 7.8 it is satisfactory. It usually shows a pH of 7.7 to 7.8. If the pH is correct, the medium is placed in the incubator for several days and if sterile is then ready for use.

The streptococcus cultured from the blood and joints by this method resembled the one Cecil considered specific for rheumatoid arthritis and showed the same agglutinating properties as his AB-13 strain. It was a Gram-positive coccus arranged in chains of 2 to 20, the length depending upon the age of the culture and the medium in which it was grown. It was bile-insoluble and did not ferment inulin. On streaked blood agar plates there was a delicate growth of grayish, smooth, isolated colonies showing a definite production of methemoglobin of a pale green shade. After 24 to 48 hours of incubation there was a narrow partially hemolyzed zone immediately surrounding the colony. Because of these intermediary qualities it has been called an Alpha prime streptococcus. The typical Alpha or *Streptococcus viridans* as found in rheumatic fever produces a much wider green zone and shows no hemolysis. Cecil called this intermediary type the "typical" strain for rheumatoid arthritis.

In the arthritis deformans group of 71 cases 46 positive cultures were obtained. In 2 cases both blood and joint fluid were positive. Therefore, 62 per cent of the cases were positive in blood or joint fluid or both.

The thirteen rheumatic fever cases yielded five positives. Three cases, malignant endocarditis, acute peritonsillar abscess and sub-acute osteitis, conditions intimately associated with rheumatic infection, were also positive for the Alpha type streptococcus.

Among the other control cases, including 17 osteoarthritis, 7 normal individuals and 47 miscellaneous diseases, only 2 were positive. These 2 cases were cavernous sinus thrombosis and one of agranulocytic angina, both of which showed Beta streptococcus.

The arthritis deformans group was composed of 52 females and 19 males. The ages ranged from 14 to 75 years, the average being 44. They were for the most part moderately advanced ambulatory cases with multiple arthritis and typical swelling of the joints. A few early cases showed only slight fusiform swelling and stiffness of the interphalangeal joints of the fingers or pain and swelling of one knee. Several were advanced cases with deformity and ankylosis and 3 were confined in bed.

A large percentage of this group of 71 cases gave a history of focal infection. Fifty-six had tonsillar, tooth or sinus infection as follows: Tonsils 24, sinuses 23, teeth 21. Twelve had a combination of two of these conditions. In 15 the tonsils were removed prior to admission, 13 had had diseased teeth extracted and in 6



of the sinus cases radical operations had been done. One case developed arthritis immediately following acute appendicitis, 1 was associated with gall bladder infection and 1 with pelvic infection. Two cases were associated with peptic ulcers and in 1 of these, cultures from the blood, the sinuses, an infected tooth and the stool were positive for the same type Alpha streptococcus.

TABLE 1.—BLOOD AND JOINT CULTURES FOR STREPTOCOCCUS.

Clinical Diagnosis. Non "rheumatic."	No. of cases.	No. of cultures.	Number negative.	Number positive.
Normal individuals . . . . .	7	8	8	0
Chronic ulcerative colitis . . . . .	2	2	2	0
Acute appendicitis . . . . .	1	1	1	0
Hypertension . . . . .	1	1	1	0
Purpura hemorrhagica . . . . .	1	1	1	0
Carcinomatosis . . . . .	3	9	9	0
Diffuse peritonitis . . . . .	1	1	1	0
Puerperal sepsis . . . . .	3	3	3	0
Typhoid fever . . . . .	1	3	3	0
Myositis . . . . .	1	1	1	0
Sciatica . . . . .	3	3	3	0
Iritis . . . . .	1	1	1	0
Neuritis . . . . .	2	3	3	0
Benzol poisoning . . . . .	1	1	1	0
Pneumonia . . . . .	1	1	1	0
Pleurisy . . . . .	1	1	1	0
Chorea . . . . .	1	1	1	0
Abscessed teeth . . . . .	2	2	2	0
Acute sinusitis . . . . .	1	1	1	0
Chronic sinusitis . . . . .	8	8	8	0
Pernicious anemia . . . . .	2	2	2	0
Chronic tonsillitis . . . . .	2	2	2	0
Myeloma . . . . .	1	1	1	0
Nephritis . . . . .	1	3	3	0
Cavernous thrombosis . . . . .	1	2	1	1
Agranulocytic angina . . . . .	1	3	2	1
Gonococcal arthritis . . . . .	4	5	5	0
(Joint fluid on 2 of above cases) . . . . .	..	2	2	0
Osteoarthritis . . . . .	17	30	30	0
Malignant endocarditis . . . . .	1	5	3	2
Acute peritonsillar abscess . . . . .	1	1	0	1
Subacute osteitis . . . . .	1	1	0	1
Total non "rheumatic" cases . . . . .	74	109	103	6
<i>"Rheumatic."</i>				
Rheumatic fever . . . . .	13	18	13	5
Arthritis deformans . . . . .	71	110	69	41
(Joint fluid on 8 of above cases) . . . . .	..	8	3	5
Total of "rheumatic" cases . . . . .	84	136	85	51

Fig. 1 illustrates the hands of a case of Still's disease. The onset was at the age of 11 years and not only the hands but also the feet were involved. Fig. 2 shows typical early extensive involvement of the hands in a young woman who suffered from the same condition in the ankles and knees. This patient showed every indication of a

profound infection and was the type that would progress rapidly toward deformity. She received intravenous vaccine for 3 months



FIG. 1.—Fusiform swelling in the interphalangeal joints of a young girl. (Still's disease.)



FIG. 2.—Typical early actively progressive arthritis deformans in the hands of a young woman.

prepared from an Alpha type streptococcus cultured from her blood and showed amazing improvement. Fig. 3 illustrates a moderately advanced case in which there was fluctuation in the interphalangeal

joints and fluid in the knee joints. The typical streptococcus was isolated from this patient's blood and vaccine was given subcutaneously for 12 months with slight improvement then 4 months



FIG. 3.—Severe moderately advanced case. Two of the interphalangeal joints contain a large amount of fluid.



FIG. 4.—Roentgen ray of an advanced condition, showing bone rarefaction and permanent deformity.

intravenously with rapid improvement. Fig. 4 shows deformity with rarefaction of the bones in the hands. This patient was 60 years of age, had suffered from the disease 15 years, every joint in her body was involved and she could hardly walk when first observed. The blood, kn  e fluid and tonsil cultures were all positive for Alpha type streptococcus. After the subcutaneous administration of vaccine for 14 months she showed remarkable improvement. The knees were straight and flexible, a great deal of motion had returned to the hands and there was improvement in every way. Fig. 5 is the photograph of a patient who was bedfast 19 years. The infection and inflammation were followed by atrophy and contracture, deformity and ankylosis.



Fig. 5.—Advanced stage of arthritis deformans. Bedfast 19 years.

The clinical course of arthritis deformans is characteristic of an infection. Occasionally the onset is acute with fever and migratory acute joint symptoms suggestive of rheumatic fever. When the onset is gradual there is insidious and progressive swelling of the joints. The patient loses weight and strength and becomes pale and chronically ill. Some of the concomitants of arthritis deformans give every appearance of metastatic infection. Two of our patients suffered from iritis prior to the development of joint symptoms.

Pathologically the joint lesions are typical of an infectious inflammatory reaction. The synovial fluid is cloudy; the synovial membrane is red, swollen and edematous; the cartilage ulcerates and the capsule becomes thickened. Microscopically the changes are those of a chronic infectious process. In a section through the synovial membrane the surface is necrotic. The underlying tissue is edematous, vascular, infiltrated with polymorphonuclear leukocytes, lymphocytes and plasma cells, and contains many fibroblasts. Finally, atrophy of the soft parts, fibrous replacement and rarefaction of the bone produce deformity and ankylosis.

The differential diagnosis of arthritis deformans and rheumatic fever usually presents no difficulties. One is acute and the other chronic, one involves the heart and the other does not, one seldom

produces deformities of joints, the other always tends toward deformity. Rheumatic fever frequently occurs in childhood, while arthritis deformans develops in the second and third decades. It is possible that arthritis deformans cases with a rheumatic fever history develop a secondary specific infection.

The bacteriologic differentiation of rheumatic fever and arthritis deformans is more difficult than the clinical differential diagnosis. In primary cultures there is usually a slight difference in the characteristics of the streptococcus found in the blood and joints of these two clinical entities. Whether the clinical difference is due to specific strains of streptococcus, to the elective action of an organism in different states of virulence for certain types of tissue, or to a difference in tissue response, cannot be explained at this time.

It is frequently difficult to differentiate arthritis deformans and osteoarthritis. In 612 cases of chronic arthritis studied in the Cornell Clinic by Cecil and Archer,<sup>10</sup> 182 (30 per cent) were classified as noninfectious osteoarthritis. In the Hospital of St. Barnabas Clinic 76 per cent were chronic infectious arthritis and 24 per cent osteoarthritis. Arthritis deformans usually affects younger people, and there is a history of focal infection. They are underweight and undernourished, have multiple arthritis, the interphalangeal and metacarpophalangeal fusiform swellings are characteristic and they develop deformities. Osteoarthritis is a disease of older people, there is no history of focal infection, they are usually overweight, Heberden's nodes are characteristic of the milder form and the knees and hips are most frequently involved. In osteoarthritis there are none of the pathologic characteristics of infection. The cartilage is at first roughened, then it becomes worn away and the underlying bone is finally laid bare. At the edge of the surface there is more or less lipping and spur formation. Obviously, the Roentgen ray examination frequently clinches the diagnosis. There are some mixed types which, without bacteriologic study, would be diagnosed only as osteoarthritis. In one of our cases there was typical lipping of the hip joint in a well-nourished woman of 60 years, from whose blood a streptococcus was isolated and whose serum agglutinated the rheumatoid streptococcus in a very high titer, 1 to 2500 dilution, and rather prompt improvement followed specific vaccine therapy.

Cecil found that patients with rheumatoid arthritis showed high agglutination for the typical strain in 94 per cent of the cases. This would be important not only in proving the specificity of the organism for this type of arthritis, but also in differentiating borderline and noninfectious types.

Agglutination tests were made in 150 rheumatoid and control cases. Sixty of the 71 arthritis deformans cases were tested, 52 showed agglutination of the rheumatoid streptococcus (AB 13 strain) and 37 in high titer 1 to 640-5120.

TABLE 2.

No. of cases.	Agglutination titer.
2 . . . . .	1 : 5120
7 . . . . .	1 : 2560
10 . . . . .	1 : 1280
18 . . . . .	1 : 640
5 . . . . .	1 : 320
3 . . . . .	1 : 160
5 . . . . .	1 : 80
1 . . . . .	1 : 40
1 . . . . .	1 : 20
8 . . . . .	0

The majority of the cases with arthritis deformans of many years' duration showed agglutination in a low dilution, if at all. One patient, already mentioned, with ankylosed joints and bedfast 19 years, showed no agglutination. Apparently the agglutination reaction is an indication that an individual is developing a resistance for streptococcal infection somewhere in the body, it may be in the sinuses, gall bladder or joints. These agglutinations run nearly parallel with those of some other diseases, namely, typhoid fever and undulant fever, in that they rarely become positive in the very early stages of the disease. They may vary in strength from week to week and finally become weaker or negative after the infection has subsided. It probably will never be as specific as the Widal reaction, because in typhoid fever the organism is in a fairly narrow group while the streptococci are heterogenous.

The specificity of the infection cannot be determined through dermal tests, because there is as yet no specific skin test for bacteria such as for horse dander in certain types of asthma. The agglutination reaction is undoubtedly of considerable value in differential diagnosis, particularly in osteoarthritis in which type vaccine is never indicated. Careful clinical study and classification of infectious types of arthritis is vitally important. The final proof of specificity at the present time must be made through cultural studies.

The treatment of arthritis deformans falls into four groups: general, focal, local and specific.

The improvement of the patient's general resistance through rest, nourishing food rich in vitamins, sunshine, rest in bed during the acute stage of the disease, medication or even transfusion if necessary for anemia and also a change in climate, are all just as important as supportive treatment in tuberculosis or any other chronic infection.

The focal treatment applies to the removal of all available primary foci such as infected tonsils, diseased teeth, sinus infections, etc. Although 60 per cent of the patients who gave a history of tonsillar or tooth infection had those foci removed before they came under our observation, nearly all of them had continued to become progressively worse. It is of interest and possibly of importance in

treatment to note that 8 patients were definitely worse after such operations, and 2 cases that prior to the removal of badly diseased tonsils had only indefinite pain developed severe forms of arthritis deformans immediately following tonsillectomy. Perhaps in such cases preliminary vaccine treatment would tend to protect the individual from an overwhelming infection.

The local treatment is chiefly corrective, including physiotherapy, hydrotherapy, massage and orthopedic treatment which applies particularly to the cases that have developed deformities.

By specific treatment is meant the use of vaccine or immune serum for the purpose of controlling an infection in the joints, which in the majority of the cases does not clear up through general or focal treatment. Unfortunately it has not been possible to develop immune serum for the treatment of this disease, but vaccine therapy is now recognized as an efficient method of attacking infection which has become established in the joints. The use of stock vaccine or of autogenous vaccine prepared from any organism which might be found in the throat, nose or stool, gives only temporary relief, if at all, and then probably through the foreign protein effect of stimulating phagocytes. This also applies to the use of typhoid vaccine, milk, etc.

The specific vaccine was prepared from the Alpha type streptococcus isolated from the patient's blood, joint fluid or foci or from typical strains in case an autogenous vaccine could not be obtained. The bacteria were killed by heating broth cultures to 60° to 65° C for 1 hour. Vaccine prepared from the blood or joint fluid is more specific than that from other sources because these organisms are heterogeneous and there may be a great variation in different strains.

The vaccine was administered subcutaneously and intravenously. The former method was used exclusively until recently when most of the cases under treatment were shifted to intravenous injections and others were started by that method. The initial dose when used subcutaneously was 100 million, increasing 200 million every week until a maximum dose of 2000 million was reached and that amount continued indefinitely. In most instances this amount produced no reaction. Larger doses were abandoned because of the frequency of joint reactions which occasionally resulted in exacerbations which continued for 2 or 3 months. In case of joint or systemic reactions with 2000 million or less the dose should be reduced. The initial intravenous dose was 100 thousand, increasing 100 thousand every 3 or 4 days to 10 million, then every 5 days to 100 million, and continuing with that amount every 7 days. The dose was increased more rapidly and to larger doses in some cases and 1000 million was reached and continued without reactions in a few cases. However, most patients complained of general discomfort or recurrent joint symptoms if the dose exceeded 100 million or if that amount was continued at frequent intervals. Two patients developed

chills and fever following 600 and 1000 million doses, and apparently improved more rapidly after that time. But in nine instances when joint reactions followed larger doses progress was apparently impeded. The improvement was more consistent and satisfactory in the absence of reactions. As a rule the dose should be smaller in acute cases than in chronic ones. However, the individual response is the most important single factor in standardizing the dosage.

Regarding the rationale of intravenous vaccine therapy Swift, Hitchcock, Derick and McEwen<sup>11</sup> demonstrated that in cases of rheumatic fever the patient was in a state of hyperergy and that this could be controlled by intravenous rather than by subcutaneous injection. A state somewhat similar to this seems to appear in arthritis deformans. Swift showed by animal experiments that injections of streptococcal vaccine into tissues tended to sensitize while intravenous injections tended to desensitize the tissues.

Another phase of intravenous treatment was suggested by Julianelle who demonstrated a striking difference in immunologic response with different methods of administration of the same vaccine. Rabbits injected intravenously with heat-killed pneumococci developed highly specialized type-specific agglutinins for this particular pneumococcus strain, together with less specialized, species-specific antibodies for other strains. When he injected the same typed vaccines intracutaneously only the semi-specialized or species-specific antibodies were formed, the type-specific agglutinins being completely absent.

Our results with specific vaccine treatment were extremely satisfactory in early and moderately advanced cases. Several of these cases that received subcutaneous vaccine for a period of 8 months to 18 months were discharged as cured and vaccine discontinued 6 to 8 months ago. These cases were becoming progressively worse, all available foci had been removed before they came to the clinic and essentially no form of treatment except vaccine was used. Some more advanced cases including the one mentioned under Fig. 4, were greatly improved and a surprising amount of function was restored to the joints. Obviously, the subcutaneous vaccine must be continued for a long time in order to obtain the desired results.

The intravenous method was followed by unexpected rapid improvement of joint symptoms and of the general appearance of the patient. This quick response may be due to "desensitization" of hyperergic tissues as suggested by Swift and his coworkers. However, only larger subsequent doses will produce an active immunity through the development of specific antibodies which control the joint infection. Although it is too early to determine how long a period is required for such immunization it will be shown later that 5 early cases which received intravenous vaccine for 3 to 4 months were apparently cured.



TABLE 3.

Classification.	No. by group.	Joints involved.	Age.	Duration.		Vaccine.										Results.		
				Years.	Months.	Subcutaneous.					Intravenous.							
						Reaction.		Autogenous.	Abn.	Duration, months.	Maximum dose in millions per cc.	Reaction.		Autogenous.	Abn.		Duration, months.	Maximum dose in millions per cc.
						Joints.	Systemic.					Joints.	Systemic.					
Group I. Advanced.	1	Polyarthritides, ankylosis knees, hips, hands	30			+	+	28	3000	+	+	+	+	+	80	...	...	Symptoms relieved, general health restored.
	2	Polyarthritides, extensive deformity	56	15		+	+	17	4000	+	+	+	+	+	100	...	...	Marked functional improvement.
	3	Polyarthritides, deformity of hands, knees	51	25		+	+	9	2000	...	...	...	...	...	50	...	...	Joint and general improvement.
	4	Polyarthritides, deformity of hands	45	20		+	+	6	1000	+	+	+	+	+	90	...	...	Joint and general improvement.
	5	Polyarthritides, deformity of hands (toxic)	44	10		+	+	5	2000	...	...	...	...	...	40	...	...	Marked improvement following intravenous.
Group II. Severe	6	Deformity in ankles, knees, hands	42	9		+	+	12	1000	...	...	...	...	...	80	...	...	Improved.
	7	Hands, knees, ankles	50	1		+	+	10	3000	...	...	...	...	...	600	...	...	Marked improvement.
	8	Hips, knees, ankles, hands	62	5		+	+	10	3000	...	...	...	...	...	34	...	...	Marked improvement.
	9	Polyarthritides (exudative)	45	1		+	+	16	3000	...	...	...	...	...	200	...	...	Cured; vaccine discontinued 6 months.
	10	Knees, ankles, hands (exudative)	45	1		+	+	16	3000	...	...	...	...	...	100	...	...	Remarkably improved.
	11	Knees, ankles, hands (exudative)	48	1		+	+	18	3000	...	...	...	...	...	...	...	...	Cured; vaccine discontinued 8 months.
	12	Hands, shoulders, ankles (exudative)	40	8		+	+	20	3000	...	...	...	...	...	...	...	...	Cured; recently discontinued.
	13	Polyarthritides (griets for 1 year)	46	3		+	+	16	2000	...	...	...	...	...	...	...	...	Marked improvement.
	14	Polyarthritides	63	1		+	+	8	1000	...	...	...	...	...	500	...	...	Marked improvement.
	15	Polyarthritides (toxic)	40	2		+	+	12	2000	...	...	...	...	...	400	...	...	Marked improvement.
	16	Knees, ankles (exudative)	52	2		+	+	12	1000	...	...	...	...	...	34	...	...	Symptomatically cured.
17	Spine, hips, knees, shoulders (toxic)	26	14		+	+	12	3000	...	...	...	...	...	200	...	...	Marked improvement.	

Group III. Advanced Cases. Moderately	1	Hips, knees	26	1½	..	..	+	+	5	1400	....	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
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The results of treatment may be summarized through the analysis of 48 cases of arthritis deformans that have received specific vaccine treatment for periods of 3 to 30 months. These were divided into five groups: advanced, severe, moderately advanced, moderately advanced, severe early and early cases.

**Group I** was composed of severe advanced cases with an average duration of 12 years' illness at the time of admission. Practically all joints were involved in these cases and more or less deformity, rarefaction of bone, atrophy of soft parts and ankylosis had developed. In Case 1 an attempt was made to straighten the knees by orthopedic surgery but ankylosis developed in the hips which only made a bad condition worse. This patient received vaccine for a period of 30 months with relief of symptoms and restoration of general health. In only two of this group were autogenous vaccines prepared from blood cultures. Case 2 received vaccine prepared from both blood and joint fluid cultures. A maximum combined subcutaneous dose of 4000 million was reached and continued several weeks when an exacerbation of the arthritis occurred which necessitated hospitalization of the patient for 2 months, following which time vaccine was resumed. However, most of the improvement occurred prior to the reaction and was not dependent upon it. This patient who had suffered from arthritis deformans 15 years and could hardly walk or move her hands when admitted regained a surprising amount of function following the absorption of peri-articular inflammation. Case 5 received relatively small doses of vaccine because of a tendency to reactions and showed very little progress until an organism was isolated from her blood and autogenous vaccine was given intravenously. Case 6, whose Wassermann was positive, failed to improve following antiluetic treatment but showed definite improvement after receiving vaccine therapy. All of these cases were improved, pain was relieved, inflammation subsided and the general condition was changed from that of a chronically ill, poorly nourished individual to one who appeared normal except for permanent deformities.

**Group II.** In this group there were 11 severe moderately advanced cases suffering from polyarthritis for periods of 8 months to 5 years. The hands, knees and ankles were most extensively involved and whereas rarefaction and atrophy were outstanding features in Group I, fluid exudate in the joints was predominant in this group. They received vaccine for periods of 2 to 20 months and in 8 of the 11 cases autogenous vaccine was used. Case 1 who could scarcely walk because of involvement of the hips showed considerable improvement following 10 months of subcutaneous vaccine in maximum doses of 3000 million. Then autogenous intravenous vaccine was used for  $3\frac{1}{2}$  months reaching a dose of 600 million when a severe systemic reaction with chills and fever developed. Prompt rapid improvement followed and the dose of 600 million

has been continued without further reaction. It cannot be determined whether this sudden improvement was the result of long continued vaccine, the chill, the intravenous method or the fact that the autogenous vaccine from her blood culture was instituted at that time. Case 8 did very well until larger doses were reached when a severe exacerbation of the joint symptoms occurred and continued for 2 months. The psychic effect of such reactions is very bad for the patient and aside from other factors is a sufficient reason for avoiding them. Case 6, now classified as cured, developed troublesome reactions on two occasions, particularly in a recurrence of iritis.

Case 4 was a very severe type that might well have been placed in the advanced group because of such extensive involvement of the knees and ankles, but remarkable improvement followed absorption of the fluid in the knees. The patient was desperately ill and unable to walk on admission. Transfusions and other supportive treatment were used and after 6 months of specific treatment she resumed work and has continued it for the past year. Case 2 was also desperately ill and will undoubtedly have some residual deformity of the hands. (Fig. 3.) Case 10 had a large amount of fluid in the knees and is now symptomatically cured after  $3\frac{1}{2}$  months of intravenous autogenous vaccine. It is also of interest that eczema, from which he had suffered for 10 years, quickly cleared after a few injections had been given. Case 3 was discharged as cured after 12 months of treatment, had a slight recurrence after 2 months, was treated again for 4 months and has now had no recurrence without vaccine for 6 months. Case 11 was a seriously ill, toxic, emaciated young man. Although the spine, hips, knees and shoulders were extensively involved, this patient pluckily continued work most of the time he was under treatment and is slowly recovering. More rapid progress would undoubtedly occur in such cases if they could afford proper hospital or sanitarium treatment. Case 5 was one of the first treated and although every joint in the hands and wrists was badly swollen and the hands were useless and apparently permanently deformed, they are now perfectly normal in appearance and function and he has had no vaccine or recurrence of symptoms for 8 months.

**Group III**, 18 in number, comprised more than one-third of the 48 cases. They were classified as moderately advanced with an average duration of 6 months to 2 years illness. Involvement of the hands and knees was most frequent. The spine was affected in 7 cases and the hips in 5. There was less exudate in the joints than in those of Group II. Three cases were associated with osteoarthritis, 2 of which had positive blood cultures, and all showed agglutination in high titer. Six of this group were discharged as cured after receiving vaccine for periods of 9 to 23 months, 4 of which had intravenous as well as subcutaneous vaccine. The vaccine

was discontinued for 1 to 5 months and no recurrences have developed. One of these cases complicated with peptic ulcer was mentioned under focal infection. The other cases were arrested or greatly improved.

**Group IV** is a very interesting one, consisting of 3 acutely ill, febrile, toxic, anemic patients. Practically all joints were acutely involved including the spine in 2 and temporomaxillary in 1, but none had cardiac involvement. Case 1 improved with remarkable rapidity on intravenous autogenous vaccine until the dose reached 200 million and an acute recurrence developed which temporarily checked the progress. Case 2 had severe involvement of the spine, hips and temporomaxillary joints. A radical sinus operation was done and after 6 months of rest and vaccine therapy the arthritis was apparently controlled when he returned to work against advice and 6 weeks later developed an alarming recurrence. The third case was treated for iritis without benefit for several months before joint symptoms developed and had extensive psoriasis practically covering the unexposed parts of his body for 5 years. He received subcutaneous vaccine for 4 months to a dose of 2000 million and intravenous vaccine for 4 months. When making the change, the preliminary small doses were not given and the initial intravenous dose was 10 million which produced a severe general; but no joint reaction. Following that the doses were rapidly increased to 1000 million which were received weekly for some time without further reaction and with rapid improvement in every way, including an unexpected clearing of the psoriasis. He has resumed work but is continuing treatment.

**Group V** was composed of 9 early cases. The duration of illness was 2 weeks to 10 months. Polyarthritis was present in 6, fingers only in 1, and knees only in 2. Subcutaneous vaccine was given in only 2 of these cases. All received intravenous vaccine for periods of 3 to 5 months, 5 being prepared from streptococci cultured from the blood. The dose did not exceed 20 million in 2 cases and reached 500 million in 2. Progress was more satisfactory in the former than in the latter. Three of this group were discharged as cured and vaccine was discontinued. Two were clinically cured with vaccine continued. The other 3 showed prompt improvement. One of the cured cases, No. 1, followed trauma (automobile accident). The knee, spine and shoulder were involved; the blood culture was positive and the agglutination 1 to 640. All symptoms disappeared after 2 months and vaccine was stopped after 4 months. The last 4 cases, 3 of which had positive cultures, were clinically cured 3 months after vaccine was started. This group was the most satisfactory because of the quick response to specific vaccine therapy. If all cases could be treated at this stage a larger percentage of cures could be reported and permanent deformities could be prevented.

**Conclusions.** 1. Our results confirm recent investigation that arthritis deformans is due to an Alpha type streptococcal infection of the joints.

2. Climate and fatigue are important predisposing factors.

3. The Alpha type or Alpha prime streptococcus causing arthritis deformans produces slight hemolysis in primary cultures.

4. The blood or joint fluid was positive for this streptococcus in 62 per cent of 71 arthritis deformans cases.

5. An improved cultural method for the quick growth of this organism from the blood and joint fluid is described.

6. The clinical picture and pathology of arthritis deformans are typical of an infectious process.

7. Agglutination tests are of considerable value in diagnosis.

8. The importance of general and focal treatment should not be underestimated.

9. Specific vaccine therapy is the most efficient form of treatment because it has cured or improved cases that were becoming progressively worse following other forms of treatment.

10. Vaccine should be prepared from blood or joint cultures when possible, otherwise from cultures from foci or from stock specific strains.

11. Vaccine treatment preliminary to the removal of foci, particularly badly infected tonsils, might prevent undesirable joint reactions.

12. Vaccine for the cure of joint infection must be continued for a long period of time.

13. Intravenous vaccine promptly relieves symptoms and probably controls the joint infection more quickly than subcutaneous injection.

14. The dose of vaccine and interval between injections should be so regulated that reactions do not occur, particularly joint reactions.

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## A STUDY OF 503 CASES OF PULMONARY TUBERCULOSIS WITH INDEFINITE OR NO USUAL ABNORMAL PHYSICAL SIGNS.\*

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THE history of the diagnosis of pulmonary tuberculosis portrays in a revealing manner what might be called the psychological opposition offered by many of us to medical advance, which unfortunately increases with age. You will recall the strong opposition to the introduction of percussion when diagnosis was based entirely upon symptoms. Broussais's opposition to Laennec and his method of auscultation is notorious. Many patients had to be sacrificed before the tubercle bacillus was definitely and widely accepted as proof of the presence of tuberculosis. Today the Roentgen ray examination in pulmonary tuberculosis is meeting with the same opposition. The same arguments that have been or were advanced against the other forward steps in the physical diagnosis of diseases of the lungs have been presented. The law that it requires at least a generation before any new medical discovery is used by the general practitioner applies here. This communication is an attempt to combat such views and to show that a new era in the diagnosis of pulmonary tuberculosis is upon us.

The widespread use of the Roentgen ray in the diagnosis of abnormal chest conditions, and especially in early pulmonary tuberculosis, has led to a reaction against the method in some quarters. It is usually more manifest among those physicians who are not actively engaged in the study and treatment of pulmonary tuberculosis. Those of us who were engaged in the struggle against tuberculosis before the advent of the Roentgen ray can recall how difficult it was to exclude pulmonary tuberculosis, how some cases ended fatally when we took the chance of excluding pulmonary tuberculosis in patients with practically no symptoms and presenting no abnormal physical signs. With this in mind many individuals

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were treated for pulmonary tuberculosis which they no doubt did not have. It was, however, impossible either to confirm or to deny the diagnosis, a condition which is more rarely present today.

If pulmonary tuberculosis were today as rare as it bids fair to be in another decade or two, the general practitioner, the consultant, the diagnostician, the specialist in other lines, especially the laryngologists and the gastroenterologists, could all be rather casual in their consideration of pulmonary tuberculosis. Unfortunately, however, such is not the case for the reduction of the morbidity from this disease has lagged far behind that of the mortality. It behooves then all concerned in diagnosis in medicine to bear constantly in mind that pulmonary tuberculosis is as protean a disease as syphilis, and no less difficult to diagnose.

Now if the tuberculous pulmonary lesion always developed in the outer second or third centimeters of the pulmonary parenchyma, where it is accessible to the ordinary methods of physical exploration, or again if it always so irritated and ulcerated the bronchial mucosa that a great excess of mucus was excreted, containing usually tubercle bacilli, the diagnosis would be greatly facilitated, for the usual methods of physical exploration of the lungs (auscultation and percussion) would reveal a pathological change. Unfortunately, such is not the case. As far back as the beginning of the century Osler, among others, recognized that extensive disease of the lungs could exist with few or no abnormal physical signs. Today all students of pulmonary tuberculosis see many cases of this nature, and I wish to present to you some conclusions I have arrived at from a study of some 503 such cases. I have the temerity to do this for within the past year some men of excellent standing have denied the possibility of the existence of pulmonary tuberculosis in students and others when it was not possible to diagnose it by the usual method of symptoms and physical signs. These cases were selected from 1900 consecutive cases at the Trudeau Sanatorium. I wish to thank Dr. Heise and Mr. Sampson for permission to publish this data.

The method by which a diagnosis of chronic pulmonary tuberculosis was established in these cases is that used for some years at the Trudeau Sanatorium. The occurrence alone of either hemoptysis of a drachm or more or of pleurisy with effusion, explainable on no other grounds, is considered to justify a diagnosis of suspected pulmonary tuberculosis in the absence of all other symptoms. In these cases of course neither the physical signs nor the Roentgen ray has proved of any aid. If, however, both of these symptoms when not otherwise explained, occur in a patient a definite diagnosis of pulmonary tuberculosis seemed justified. The occurrence of moderately coarse râles or of a parenchymatous Roentgen ray lesion (mottling, irregularly distributed) above the third rib and third vertebral spine was considered sufficient evidence for a posi-



tive diagnosis of pulmonary tuberculosis until disproved. Tubercle bacilli in the sputum in the absence of lesions above the trachea must be considered as absolute proof of pulmonary tuberculosis which today no one questions.

The incidence of these 5 cardinal diagnostic data in 1367 cases diagnosed pulmonary tuberculosis from 1478 consecutive cases admitted to the Trudeau Sanatorium are as follows:

	Per cent.
Tubercle bacilli . . . . .	61.5
Râles . . . . .	68.5
Roentgen ray . . . . .	99.0
Hemoptysis . . . . .	33.5
Pleurisy . . . . .	12.0

During the past year Mr. Sampson has reclassified 1472 cases at the Trudeau Sanatorium, using the present classification based mainly upon the Roentgen ray examination. "Of the suspects of the original classification only 15 per cent remained in this group, while 71 per cent were transferred to the nontuberculous and 13 per cent to the minimals. Of the former minimals 33 per cent remained in the group, 26 per cent were transferred to the nontuberculous, 11 per cent to the suspected, and 28 per cent to the far advanced. The former moderately advanced group were least affected but 20 per cent of the former far advanced group were transferred to the moderately advanced."

Negative evidence is never as satisfactory as evidence upon the positive side. However, some years ago Dr. Heise and I attempted to prove the value of the five criteria in the diagnosis of pulmonary tuberculosis. We studied 264 cases in which pulmonary tuberculosis had been excluded by this method, following them over a period of 1 to 7 years. All these patients had been sent to the Trudeau Sanatorium with a diagnosis of pulmonary tuberculosis. In 61 of them, on account of hemoptysis or an attack of pleurisy with effusion without discoverable cause, we made a diagnosis of suspected pulmonary tuberculosis. After 2 to 7 years 2 of these developed pulmonary tuberculosis but 1 had had a tuberculous cervical adenitis and another tuberculous caries of the rib while under our care. Of the remaining 203 patients none developed pulmonary tuberculosis. In all of these patients of course no parenchymatous change on the film was present and except in the 2 mentioned none developed pulmonary tuberculosis, though as I said, a diagnosis of pulmonary tuberculosis had been previously made.

It may be of interest to note in passing that after many years of study we are only now beginning to discover when, at what age, pulmonary tuberculosis really begins. This knowledge has come to us through the study of many thousands of school children. For instance, in Saranac Lake the entire school population has had pulmonary radiograms taken each year for the last 5 years. We

have undertaken this work in order to determine if possible when pulmonary tuberculosis first appears, first develops in the lungs. In such a small number of individuals, between 1400 and 1500, the number of cases of positive, definite pulmonary tuberculosis are so few that we have not yet felt justified in drawing any definite conclusions. I might say, however, that the number of positive cases of the adult type of pulmonary tuberculosis is little if any larger than that found in the general population of the country. On the other hand, as a large number of the parents of the children studied came to Saranac Lake to take treatment for pulmonary tuberculosis, more of the children presented what is known as the primary complex, that is calcified nodules occurring in the pulmonary parenchyma and hilum glands, than occurs in the general population. We are not convinced that the adult type occurs more frequently in children who have presented the childhood type just mentioned. We have a growing feeling that evidence of pulmonary tuberculosis which is going to occur later in life can usually be detected by careful roentgenologic study before or at the twentieth year. To put it another way, if at the twentieth year good stereoscopic films present no evidence of pulmonary tuberculosis, no parenchymatous changes, the chances are very slight that that individual will ever suffer from pulmonary tuberculosis.

This brings to mind that interesting group of individuals who present definite evidence of pulmonary tuberculosis on roentgenologic examination with no history of any illness to explain it. These persons, occurring usually among groups of employees, students, or of children subjected to routine roentgenologic examination, need careful watching but no treatment. By careful watching I mean repeated Roentgen ray examinations at intervals of 6 to 12 months, for in no other way can in many of them a slight advance be detected and activity of the disease determined. I imagine the diagnosis of quiescent or arrested pulmonary tuberculosis in this group is what has aroused some of the opposition to the use of the Roentgen ray in diagnosis.

The significance in the diagnosis of pulmonary tuberculosis of definite changes (moderately coarse râles) detectable by physical examination at the apex of a lung may still be questioned by a few but the importance of slight roentgenologic changes or indeed fairly well pronounced mottling in the upper third of the lung is still questioned by many. This is the problem that needs to be settled though I doubt if it can be done quickly. To attempt to aid in this I planned to study the further course of the disease in a group of 503 patients at the Trudeau Sanatorium who presented on the first examination slight or no abnormal physical signs and in whom the diagnosis of chronic pulmonary tuberculosis which was made depended largely or in some instances almost wholly upon the Roentgen ray examination.

The 503 patients included 159 in the minimal stage, 322 in the moderately advanced, and 22 in the far advanced. They were selected from 1900 consecutive cases admitted to the institution between July, 1920, and April, 1927, that is from 8 to 4 years before the study was undertaken. All had had a previous diagnosis of pulmonary tuberculosis. In all of them abnormal physical signs were absent or if present were insufficient for a definite diagnosis of pulmonary tuberculosis.

You may recall that among the five criteria mentioned in connection with the diagnosis of pulmonary tuberculosis râles, fine or more frequently moderately coarse, in the upper third of the chest were emphasized. None of these cases had such râles, and only 1 or 2 had a few râles at the very base of the lung called by some atelectatic, by others marginal. In the vast majority the slight changes consisted chiefly in connection with breathing and vocal resonance. A rather large percentage of the patients who gave a history of pleurisy with effusion had definite abnormal physical signs at one or the other base but no râles. In other words, all changes which have been considered characteristic of pulmonary tuberculosis were lacking.

The roentgenologic examination, however, revealed in every case changes which were interpreted as being caused by pulmonary tuberculosis, *i.e.*, apical Roentgen ray lesion, usually in the upper third of the lung field. The problem then was how correct was this diagnosis based, it might be claimed, entirely upon the film, for all these films presented such a parenchymatous change.

The next step logically was the examination of the sputum. Of the 503 cases 298 (59 per cent) had tubercle bacilli in their sputum at some time, and as this is universally assumed to be proof positive of the presence in such cases of pulmonary tuberculosis, we need not further consider them. But it must not be overlooked that in many, tubercle bacilli were found in the sputum only after a lapse of some months after the diagnosis had been made.

#### RESULTS OF THE SPUTUM EXAMINATION FOR TUBERCLE BACILLI.

	Positive.	Positive only previous to admission.	Negative on admission, positive later.	Negative.
Minimal . . . . .	52	18	24	107
M. A. . . . .	226	56	66	96
F. A. . . . .	20	0	3	2*
Total . . . . .	298 (59%)	74 (25%)	93 (18%)	205 (41%)

\* Both had intestinal tuberculosis.

Of the remaining 205 patients, 2 were classified as far advanced on account of the presence of tuberculous colitis. If we should attempt to classify them upon their pulmonary findings both would fall into the moderately advanced group. It is of interest to note that one of them died later from pulmonary tuberculosis and the



FIG. 1.—No. 71828. *R*, small amount of infiltration to 1 *R*. and 3 *V.S.*; *L*, infiltration to 3 *R*. and 5 *V.S.* Small cavity in this region. Physical findings negative.



FIG. 2.—No. 73257. *R*, small amount of infiltration to 2 *R*. and 4 *V.S.*; *L*, infiltration to 4 *R*. and 7 *V.S.* Pleurisy with diaphragmatic adhesion. Physical findings negative.

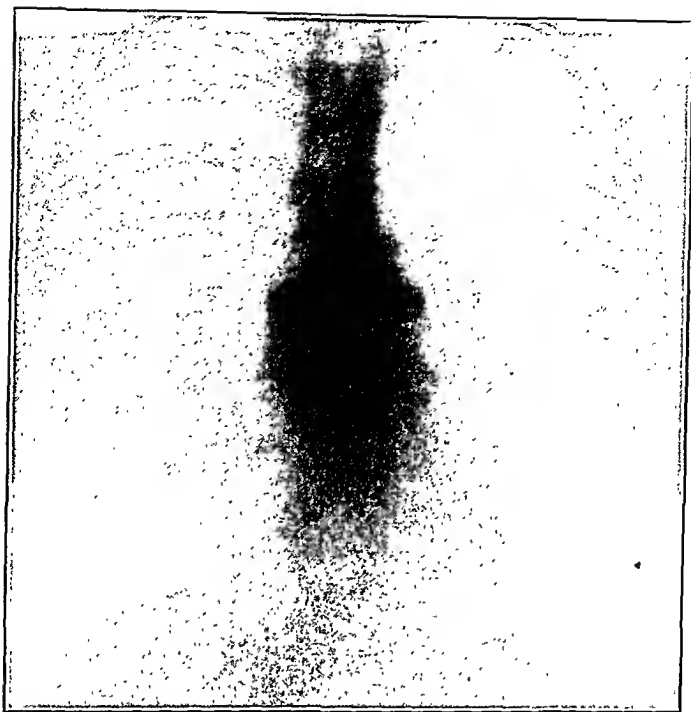


FIG. 3.—No. 75238. *R*, infiltration quite suggestive of old foci to 5 *R*. and 6 *V.S*. A few isolated tubercles in the root region; *L*, small amount of infiltration quite suggestive of old foci to 2 *R*. and 4 *V.S*. A few isolated tubercles in the root region. Physical findings negative.

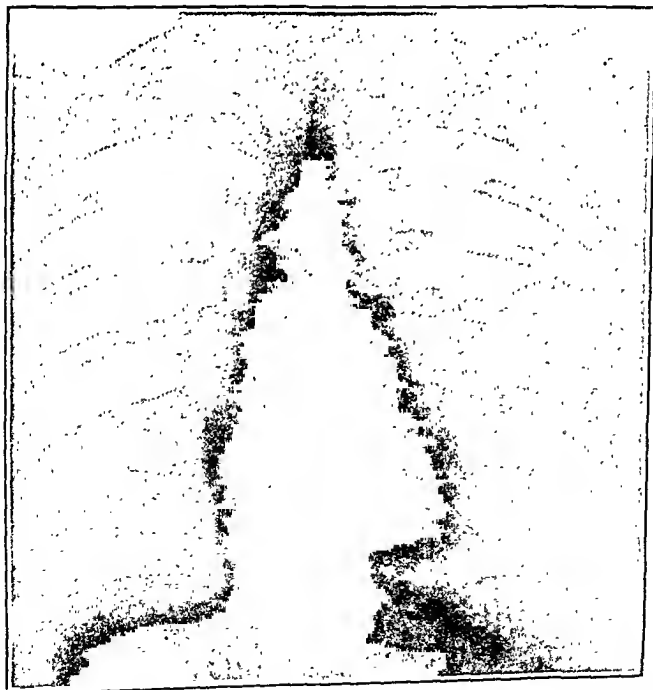


FIG. 4.—No. 77657. *R*, small amount of scattered infiltration more or less throughout; *L*, infiltration to 4 *R*. and 5 *V.S*. Small cavity in the apex. Physical findings negative.

other developed definite moderately coarse râles at an apex. Now as has been already stated the presence of râles at an apex in the type of patients we are considering is usually accepted as the best evidence obtainable from physical signs of the presence of pulmonary tuberculosis, accordingly we studied the remaining 205 patients to see if any others developed such râles. Thirty-six patients did develop such râles and 169 did not. Consequently we concluded that these 36 patients had pulmonary tuberculosis and turned our attention to the 169 who failed to develop râles. One of them was, as noted previously, in a far advanced stage on account of tuberculous colitis and died from tuberculosis.

## DEVELOPMENT OF RÂLES ON LATER EXAMINATION IN 205 PATIENTS.

	Râles developed.	No râles developed.
Minimal . . . . .	12	95
M. A. . . . .	23	73
F. A. . . . .	1	1
	<hr/>	<hr/>
Total . . . . .	36	169

Another of the diagnostic criteria which we have mentioned is hemoptysis and the remaining 168 patients were studied to see if blood spitting of a drachm or more had occurred in the course of their disease. Sixty-three patients had had such hemoptyses and we consequently decided that under the conditions mentioned that they also had pulmonary tuberculosis.

## OCCURRENCE OF HEMOPTYSIS IN 168 PATIENTS.

	Hemoptysis occurred.	Hemoptysis absent.
Minimal . . . . .	34	61
M. A. . . . .	29	44
	<hr/>	<hr/>
Total . . . . .	63	105

Pulmonary tuberculosis is a relapsing disease and if these patients had had pulmonary tuberculosis we should expect a certain number to relapse. Accordingly the 105 patients in whom we have not yet verified the diagnosis of pulmonary tuberculosis were studied. They have been followed very carefully since their discharge from the institution and 8 have died (5 from pulmonary tuberculosis, 1 each from splenomyelogenous leukemia and intestinal obstruction, and 1 following an operation for appendectomy). Twenty-one have suffered relapses at one time or another. This evidence was accepted as verifying in all probability the previous diagnosis of pulmonary tuberculosis in 26 more patients, leaving us still to consider 76 patients.

## CONDITION AFTER DISCHARGE OF 105 PATIENTS.

	Well.	Relapsed.	Died.
Minimal . . . . .	46	11	4 (2 with pulmonary tuberculosis)
M. A. . . . .	30	10	4 (3 with pulmonary tuberculosis)
	<hr/>	<hr/>	<hr/>
Total . . . . .	76	21	8

Another criterion diagnostic of pulmonary tuberculosis is pleurisy with effusion, and a study of the 76 patients who remained well revealed that 20 of them had had pleurisy with effusion, 10 among the minimal group and 10 among the moderately advanced. In such patients I felt that a positive diagnosis of pulmonary tuberculosis was justified. If you will accept such methods of diagnosis, and I personally am convinced that they are correct, we have left for further consideration 56 patients, 36 falling in the minimal group and 20 in the moderately advanced.

I feel a little doubtful in asking you to accept what I believe to be correct, namely, that from many films it is possible to determine fairly accurately whether or not the pulmonary tuberculous lesion is active or quiescent. I realize that this is even a more difficult matter than the diagnosis of the disease for the reason that lesions lying under a rib or behind the heart may be overlooked. To attempt to determine the activity of a lesion in such a manner a few points in technique must be observed. In the first place the exposure of the films must not be longer than  $\frac{1}{15}$  of a second. Again the stereoscopic image must be good and a stereoscope must be constructed with prisms and not with the usual mirrors which often give a double image. The final requirement for such work, really a *sine qua non*, is the employment of a revolving stereoscope with windows or compartments for 4 or 6 pairs of films. Without a revolving stereoscope it is impossible to compare similar small areas on two sets of films with any degree of accuracy. Failure to follow such careful technique leads many otherwise excellent roentgenographers and students of pulmonary tuberculosis to deny that it can be done.

Among the 56 cases, 6 of the minimal and 2 of the 20 moderately advanced group had clean-cut mottling at the apex, interpreted as arrested tuberculosis. Of the 6 minimal cases 4 had suggestive abnormal physical signs with cough and expectoration in 2 (1 had nightsweats), and 2 had no cough or expectoration (1 had dry pleurisy). Of the 2 without any abnormal physical signs 1 had cough and expectoration with dry pleurisy, and 1 had neither but did have nightsweats. The 2 moderately advanced cases in this group presented in 1 cough, expectoration, and nightsweats, and in the other only dry pleurisy. Of the remaining 30 minimal cases 19 had suggestive physical signs and 11 none. Of the 19, 15 had cough and expectoration, 7 dry pleurisy, 6 nightsweats, 2 cough, only and 2 neither cough nor expectoration. Of the 11 without any abnormal physical signs 4 had cough and expectoration, 4 cough only, and 3 had neither. Four had nightsweats and 2 dry pleurisy. Of the 18 patients in the moderately advanced stage in this group 11 had abnormal physical signs, 7 normal. Of the 11, 8 had cough and expectoration, 2 cough only and 1 neither. Four had dry pleurisy and 4 nightsweats. Of the 7 without abnormal physical signs 6 had

cough and expectoration, 1 cough, only 1 dry pleurisy and 5 night-sweats. In brief, of the 48 patients with apparently active disease as interpreted on the films, 33 had cough and expectoration, 9 had cough, 6 had neither, 14 had dry pleurisy, 19 had night-sweats.

Before the introduction of the Roentgen ray such evidence as I have mentioned was commonly assumed to be sufficient for the diagnosis of pulmonary tuberculosis in most cases, like the 30 who presented some physical signs. In the 18 the diagnosis was often held in abeyance, in some instances to the regret of all parties. (I should like to show you a few lantern slides to show you upon what roentgenologic data we based our diagnoses.)

**Summary.** From the data here presented I am inclined to attribute considerable importance in the diagnosis of pulmonary tuberculosis to the Roentgen ray examination. I am convinced it will reveal the lesions of the disease long before it is manifested in any other way, for the symptoms may be so slight that they escape notice. To refuse to accept this evidence places upon those who assume such an attitude the same responsibility as fell upon those who refused to accept the importance of the tubercle bacillus or of hemoptysis or of pleurisy with or without effusion in the diagnosis of pulmonary tuberculosis. If this attitude prevails, many patients will probably relapse and pass from the assumed indefinite stage to the far advanced with slight chances of arrest and still slighter of recovery.

We are in a new era in regard to the diagnosis of pulmonary tuberculosis and whether the value of the Roentgen examination is accepted now or postponed for a decade or longer the diagnostician and roentgenographer will eventually have to modify their practice and their technique to conform with it.



## REVIEWS.

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SIXTY CENTURIES OF HEALTH AND PHYSICK. By S. G. BLAXLAND STUBBS and E. W. BLIGH, with an Introduction by SIR HUMPHRY ROLLESTON, BART., G.C.V.O., K.G.B., M.D., HON. D.C.L., LL.D., D.Sc., Regius Professor of Physic in the University of Cambridge. Pp. 253; 101 illustrations; 1 colored. London: Sampson Low, Marston & Co., Ltd., 1931. Price, 15/-. American Publisher: Paul B. Hoeber, Inc., New York City.

HERE we have the rare combination of the bibliophile who not only contributes his bit by redistributing choice medical volumes but so profits by their transient stay with him that he can write interestingly and profitably on the whole subject. The collaborating authors give an excellent word picture, augmented by 100 skillfully chosen illustrations, of the progress of ideas since prehistoric times in the long quest for health. The spirit of the various epochs, rather than the detailed century by century progress, has been sought and captured. Limiting their survey to the confines of the old-fashioned word "physick," they are able, without in any way competing with standard histories of medicine, to give an adequate portrayal of what now passes by the misleading term "internal medicine." The following table of contents gives an idea of the scope of the work and a hint at the freshness of the point of view: Primitive Notions of Health and Disease; Achievements and Superstitions of Sumerians, Babylonians and Assyrians; Ancient Egypt: Promise Limited by Magic; Beginnings of Western Science: Cretan Hygiene and Greek Medical Schools; Greece: Hippocrates, Father of All Medicine; Inheritors of Hippocrates: Alexander and Rome to 200 A.D.; A Thousand Years of Darkness: Europe 200 to 1200 A.D.; The Dry Bones Stir and Learning Awakes: 1200 to 1450 A.D.; Foundation of the Modern Period of Medicine: 1450 to 1600 A.D.; The Enemies of Man: Plague and Epidemic; Science in the Seventeenth Century: The Royal Society, Sanctorius and Harvey; New Schools of Thought: Chemistry and Mathematics in Medicine; The Microscope and the Discovery of Germs; A Basis of Modern Pneumotherapy: First Researches in Breathing; Thomas Sydenham, the Master of Clinical Medicine; The Eighteenth Century, an Era of Hygiene; Eighteenth Century Influences on Modern Medicine; Inoculation and the Beginnings of Immunization; The Growth of Hospitals and the "Sanitary Idea;" Notes on the Epoch of Modern

While it is obviously impossible to follow here the argument in any detail, a few illustrative observations and deductions are permissible. "The conclusion seems justified that a recognition of just two physical types is necessary in the formulation and development of the problem of variability in personality and form among normal human individuals"—the older linear or long-headed type and the lateral or wide-headed type.

In explanation of man's intellectual achievement, considered his most striking deviation from his nearest relative, two developmental inhibitions are offered. (1) The retention of the head proportions of the fetal stages of the highest mammals; (2) an exaggerated prolongation of the postnatal stages of immaturity. In following the development of physical constitution upon which characteristic personality depends, similarity of human to various animal types is emphasized in a way strongly reminiscent of Lavater's comparisons of over a century ago, but now with evidential basis.

It is surely an encouraging sign that publishers even occasionally prefer the sober presentation to the laity of a subject so easily capable of lurid mistreatment. E. K.

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MEDIZINISCHE PRAXIS. VOL. XII: HERZ- UND KREISLAUF-IN-SUFFIZIENZ. By DR. K. F. WENCKEBACH, Em. Vorstand der I. Medizinischen Universitätsklinik, Wien. Pp. 120; 7 illustrations. Leipzig: Theodor Steinkopff, 1931. Price, geheftet R.M. 8.00, gebunden R.M. 9.50.

THIS is the twelfth booklet of a practical series of medical treatises designed for the further education of students, practitioners and embryo specialists. Earlier titles of the series are on Endocrine Diseases (Curschmann), Gastric Ulcer (Ohnell), Asthma (Klewitz), Biliary Tract (Korte), Radiotherapy (Gudzent), so-called Rheumatism (Bauer) and Metabolic Disorders (Leschke).

The author first considers the hydrodynamic effects of various circulatory obstructions such as pericardial and valvular lesions, myocardial insufficiency, collapse, blood pressure changes and angina. In the second shorter part such auxiliary factors as "the peripheral heart," water metabolism, edema, blood volume and velocity, cyanosis, dyspnea and digitalis therapy are taken up. The freshness of the treatment is shown by the fact that only 4 of the 35 references precede the year 1925. On the other hand, the work of Douglas and Baldane, Blumgart, Heymans and Wybauw are the only non-German references given. The interesting though rather difficult text, the author's high reputation and the moderate price all should commend the book to American readers.

E. K.

REMBRANDT. By DR. J. G. DE LINT. Pp. 115; 64 illustrations. The Hague: J. Philip Kruseman, 1931. Price, \$2.50.

THIS is the first series of monographs intended to collect and analyze all the works of the Dutch painters of the seventeenth and eighteenth centuries that possess a medical interest. Rembrandt's paintings, engravings and drawings from widespread sources have been passed in review by a well-known Dutch student of medical history and some 64 here reproduced. Nearly every field of medicine is represented. Though the Dutch had largely adopted Protestantism at this time, so that paintings as church decorations no longer were demanded, nevertheless Biblical scenes were popular topics, and whether depicting miracles, birth or death scenes, contain much of medical interest. Portraits of physicians and medical scenes from Dutch daily life furnish the majority of the remainder of the topics treated. Tipped-in reproductions are used to advantage. We hope that this series, so worthily begun, will have a great and well-merited success.

E. K.

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CLINICAL ELECTROCARDIOGRAPHY. By SIR THOMAS LEWIS, M.D., F.R.S., D.Sc., LL.D., F.R.C.P., C.B.E., Physician of the Staff of the Medical Research Council; Physician in charge of Department of Clinical Research University College Hospital. Pp. 128; 107 illustrations. Fifth edition. London: Shaw & Sons, Ltd., 1931. Price, 8s, 6d.

EVEN though electrocardiography has taught much about heart disease that can now be recognized by the five senses, it still remains true that "cases of structural heart disease are few in which an electrocardiographic examination is superfluous." This treatment of the subject by its chief pioneer remains the best small book that we have about it, especially if used, as the author suggests, as an auxiliary to his larger book.

E. K.

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RESISTANCE TO INFECTIOUS DISEASES. By HANS ZINSSER, M.D., Professor of Bacteriology and Immunity, Medical School, Harvard University. Pp. 651; illustrated. Fourth edition completely revised and reset. New York: The Macmillan Company, 1931. Price, \$7.00.

"THE fourth edition of *Infection and Resistance* (see this Journal, 1923, 166, 1906) is being brought out under the new title of *Resistance to Infectious Diseases* because immunology has grown considerably closer to the interest of the physician occupied with infectious diseases than it was when earlier editions were published.

"Since the last edition was published there have been profound changes in immunologic conceptions, owing to the great advances made in the chemistry of antigens, and in the introduction of chemical and physical methods into the study of antigen-antibody reactions. The knowledge of haptenes such as the carbohydrate fractions of bacterial antigens and the lipoid fractions of heterophile antigens, together with the precise studies of Wells and Landsteiner in particular, have made it possible considerably to simplify theoretical conceptions. Much that is of pure historical interest has been abbreviated and technical details have been omitted in many cases.

"Due to the many changes in the subject, the section on anaphylaxis and hypersensitiveness have been completely rewritten. More attention has been given to analysis of the immunologic principles underlying the biology of the more important infectious diseases."

E. K.

GENEESKUNDIGE KUNSTKALENDER VOOR HET JAAR 1931. 25 illustrations. The Hague: J. PHILIP KRUSEMAN. Price, \$1.50.

THIS Medical Art Calendar has ever since the World War been a favorite with many interested in medical history. There are 27 8 x 10 inch fortnightly sheets with a memorandum space for each day at the bottom, the major space being occupied by really excellent reproductions of medical paintings, loosely tipped in. For each is given in Dutch and English the title, painter (with dates), present location, a short account of the work and its author. These informative notes have been furnished by Sikkel, de Lint and Van Gils. Further to entrance the value of this production, the pictures reproduced in former years can be bought for fl. 4.50 or fl. 50. (\$20.00) for the whole series. They are well worth it. E. K.

EYE, EAR, NOSE AND THROAT FOR NURSES. By JAY G. ROBERTS, PH.G., M.D., F.A.C.S., Licentiate, American Board Otolaryngology. Pp. 213; 102 illustrations. Philadelphia: F. A. Davis Company, 1931. Price, \$2.25.

It is the author's wish in writing this book to "bring to the nurse in training as well as to the graduate, such a conception of diseases and operations of the eye, ear, nose and throat, as will enable her to give to the specialist in these diseases the same aid and assistance, and to the patient the same care and skill, that she has so long exhibited in the field of medicine and surgery."

The experience of 20 years in head surgery and a great interest in nursing education are evident as one reads this book. It begins with the essential material covering hygiene, anatomy and diseases of the eye, ear, nose and throat. Then the surgery of these structures is carefully outlined as to the preparation of patient, anesthesia, instruments used in the operation and the "After Care."

There is one chapter on drugs and formulæ used generally by these specialists; one on the value of antiseptics, one on bacteria concerned in diseases of the eye, ear, nose and throat; one covering the "Don'ts" for nursing these patients and finally one on emergencies, met with at times, in this kind of work.

A glossary and index complete this text for which there is a need especially in schools where there is not sufficient time allowed for this important material.

M. S.

## BOOKS RECEIVED.

### NEW BOOKS.

*The Surgical Clinics of North America (Mayo Clinic Number—August, 1931).* Pp. 211; 74 illustrations. Philadelphia: W. B. Saunders Company, 1931.

*Memorie e Comunicazioni Scientifiche (1894-1930).* By PROFESSOR CESARE SERONO, Dottore in Medicina ed in Chimica, Docente di Chimica e Microscopia Clinica Nella R. Università di Roma. Pp. 701. Rome: Istituto Nazionale Medico Farmacologico Serono, 1931.

*Dynamic Retinoscopy.* By MARGARET DOBSON, M.D., Lond. Pp. 56; 11 illustrations. New York: Oxford University Press, 1931. Price, \$2.50.

*Les Poisons du Bacille Tuberculeux et les Réactions Cellulaires et Humorales dans la Tuberculose.* By DOCTEUR JEAN ALBERT-WEIL, Chef de Clinique Médicale adjoint à la Faculté de Médecine de Strasbourg; Ancien Interne des Hôpitaux de Strasbourg. Preface by PROFESSEUR A. BORREL. Pp. 327; illustrated. Paris: J.-B. Baillière & Fils, 1931.

*Nosokomeion. Quarterly Hospital Review.* First Special Number, containing the reports presented to the Vienna Congress. Pp. 492. Stuttgart: W. Kohlhammer. Price, 15 Marks.

*Publications of the Committee on the Costs of Medical Care: No. 9. A Survey of the Medical Facilities of the City of Philadelphia, 1929.* By NATHAN SINAI, D.P.H., and ALDEN B. MILLS of the Research Staff of the Committee on the Costs of Medical Care. Pp. 298. Chicago: University of Chicago Press, 1931. Price, \$1.50.

*Publications of the Committee on the Costs of Medical Care: No. 11. The "Municipal Doctor" System in Rural Saskatchewan.* By C. RUFUS ROREM, Ph.D., C.P.A., of the Research Staff of the Committee on the Costs of Medical Care. Pp. 84. Chicago: University of Chicago Press, 1931. Price, \$1.00.

*Progressive Medicine, Vol. III. September, 1931.* Edited by HOBART AMORY HARE, M.D., LL.D., Professor of Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College; Assisted by LEIGHTON F. APPELEMAN, M.D., Instructor in Therapeutics, Jefferson Medical College. Pp. 315; 17 illustrations. Philadelphia, Lea & Febiger, 1931.

*Mitteilungen des Wissenschaftlichen Komitees zur Erforschung und Bekämpfung der Kreislaufstörungen.* Pp. 26. Leipzig: Theodor Steinkopff. Price, Mark, 1.50.

The first number of an "occasional publication of the Kerckhoff Institute of Bad Nauheim."

*Paying Your Sickness Bills.* By MICHAEL M. DAVIS. Pp. 276. Chicago: University of Chicago Press, 1931. Price, \$2.50.

*Medizinische Wissenschaft und Werktätiges Volk.* By DRs. ASCHOFF, BIER, HIS, v. KREHL, v. MÜLLER, RUBNER, SAUERBRUCH and THOMAS. Pp. 216; illustrated. Berlin: Notgemeinschaft der Deutschen Wissenschaft, N.D.

Interpretations to the laity of various medical trends of immediate practical importance by leading authorities.

## NEW EDITIONS.

*The Diagnosis and Treatment of Venereal Diseases in General Practice.* By L. W. HARRISON, D.S.O., M.B., CH.B., F.R.C.P.E., Brevet Colonel R.A.M.C., and K.H.P. (Ret.); Director of Venereal Department, St. Thomas' Hospital. With a chapter on The Medico-Legal Aspects, etc., by F. G. CROOKSHANK, M.D., F.R.C.P., etc. Pp. 567; 79 illustrations. Fourth edition. New York: Oxford University Press, 1931.

*A Manual of Clinical Laboratory Methods.* By CLYDE LOTTRIDGE CUMMER, PH.B., M.D., F.A.C.P., Instructor in Dermatology and Syphilology, School of Medicine, Western Reserve University. Pp. 583; 173 illustrations. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1931. Price, \$6.75.

In this new edition the section on the Kahn reaction has been expanded and a section has been added describing Kline's reaction. Silver impregnation methods for treponemata have been included, as have the Alzheimer method for studying the cellular contents of the spinal fluid, newer methods of demonstrating oxydase granules, Newcomer's method for determining the hemoglobin content of the blood, and others. Dr. Cummer has also added descriptions of cistern puncture, the icterus index, the alcohol test-meal, the sedimentation of red blood cells, the use of histamine in studying the secretion of hydrochloric acid by the stomach, diagnosis of granuloma inguinale, the Queckenstedt test on the spinal fluid, agranulocytic angina, acute infectious mononucleosis, Schilling's simplified method for the Arneht count, leukocyte fragility, agglutination test for tularemia and undulant fever, and has revised the references to bile salts and pigments. A thorough revision of the chapters dealing with blood counting and the histology and pathology of the blood and anemias has been made by Dr. R. D. Leas, of Western Reserve University.

*The Practice of Medicine.* By A. A. STEVENS, A.M., M.D., Professor of Applied Therapeutics in the University of Pennsylvania. Pp. 1150; illustration. Third edition, entirely reset. Philadelphia: W. B. Saunders Company, 1931. Price, \$8.00.

An extensive revision has been necessitated by the many advances made since the appearance of the second edition in 1926.

*Gonorrhea in the Male and Female.* By P. S. PELOUZE, M.D., Associate in Urology and Assistant Genito-urinary Surgeon at the University of Pennsylvania. Pp. 440; 92 illustrations. Second edition, revised. Philadelphia: W. B. Saunders Company, 1931. Price, \$5.50.

To those who know the author's long experience with gonorrhea and his free disregard of unworthy idols the success of this book comes as a matter of course. His simple commonsense interpretations have been cherished—now fortunately he adds new chapters and more supporting evidence (hence the change in title)—which should carry conviction to a wider range of readers and add permanence to the value of his book.

*A Text-book of General Bacteriology.* By EDWIN O. JORDAN, PH.D., Professor of Bacteriology in the University of Chicago and in Rush Medical College. Pp. 819; 200 illustrations. Tenth edition, entirely reset. Philadelphia: W. B. Saunders Company, 1931. Price, \$6.00.

Ten editions in 23 years more or less speak for themselves.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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**Acute Monocytic (Histiocytic) Leukemia.**—COOKE (*Lancet*, 1931, 221, 129) reports that there have been apparently 18 cases of acute monocytic leukemia and describes still another case. In this instance the patient was a boy, aged 19 years, who was taken sick apparently about 2 months before the fatal ending. When seen by the author 10 days before death he was found to be markedly pale, had some epistaxis, and bleeding from the gums, which were swollen and granular. The spleen was enlarged 3 inches below the costal margin, but there were no enlargements of the superficial glands nor any particular evidence of hemorrhage aside from those from the mouth and nose. The white cells numbered 49,800, 87 per cent of which were oxidase-negative monocytes, which type cell was identical with the histiocyte, elasmocyte and monoblast of various writers. The condition clinically of monocytic leukemia does not differ from the other acute leukemias. It is only by study of the type of cell that the diagnosis can be made. Assuming that the phyletic theory is correct, there is no reason to believe that there may not be a reticuloendotheliosis which gives rise to a third type of acute leukemia comparable in every respect to the myeloid and the lymphatic types. It is rather a coincidence that in the same issue of the journal, in the reports of medical societies, there should have been an abstract of a paper on monocytic leukemia that Clough presented at the meeting of the Association of American Physicians. The condition is extremely rare, as can be inferred from the fact that Clough finds reports of only 16 cases and the author of 18. In Clough's case, in addition to the immature cells which showed the finely reticulated nuclear structure typical of monocytes, together with the grayish-blue cytoplasm and the reddish-lilac granules, there was also additional information obtained from the postmortem examination,

which unfortunately was not obtained in the author's case. At autopsy of the case "there was a very widespread leukemie infiltration of the tissues with reticulum cells that exactly resembled the monocytes in the blood." There were observed also changes in the endothelium and vascular space of the spleen. Both of these two writers believe that the disease is a distinct syndrome, but Clough, while stating that it is a distinct systemic disease, calls attention to the fact that there is often perverted activity of other parts of the hematopoietic system.

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**Effect of Brain Diet in Pernicious Anemia.**—Liver, kidney, spleen and stomach have all been organs which have been used to evoke a reticulocytic response when fed to patients suffering from pernicious anemia. UNGLEY (*Lancet*, 1931, 221, 63) reports upon the use of brain diet and gives a record of 7 patients he studied, 4 of whom had pernicious anemia and 3 of whom had a simple achlorhydric anemia. The amount of brain substance given varied from 240 to 480 gm. a day. A reticulocytic rise occurred in each of the 4 cases of pernicious anemia. The effect on the other 3 cases in 1 instance was mildly positive and negative in the other 2. He believes that the hematopoietic potency of ox brain in pernicious anemia is approximately one-third that of ox liver, drawing his conclusions from this small number of cases. He does assume, moreover, without any very good evidence that such is the truth, that the efficacy of brain itself is greater than liver in patients who show neurologic lesions.

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**The Relation of Achlorhydria to Pernicious Anemia.**—The various studies which have been made in the last few years on pernicious anemia have naturally aroused considerable interest, both investigative and speculative, on the cause of pernicious anemia and the bearing that achlorhydria may have on the pathogenesis of this blood disorder. MOSCHCOWITZ (*Arch. Int. Med.*, 1931, 48, 171) reviews certain aspects of the achlorhydria which go with pernicious anemia, the diagnosis of which is not valid unless this finding is present. From the evidence that he has been able to obtain from the literature this author believes that achlorhydria does not result from the disease but is a primary finding which occurs in a comparatively small percentage of apparently normal people, the percentage increasing with each decade. The absence of free hydrochloric acid occurs in certain families, but it is not by any means indicative that all members of the family will develop pernicious anemia. However, as a certain few do so, the condition may be described as being relatively frequently hereditary and familial, but whether or not it depends upon definite Mendelian characteristics cannot be determined at present, certainly not until at least three generations may be studied with regard to the gastric acidity and the blood count. Further statements that the author makes include one to the effect that *Bothriocephalus latus* probably does not cause pernicious anemia but rather that this particular parasite is found from time to time in the intestinal tract of people who have Addisonian anemia; it is a coincidence rather than an etiologic agent. It has never been definitely proven that pernicious anemia occurs after gastric resection with its associated achlorhydria. Some of the severe anemias of pregnancy are probably cases of pernicious anemia in individuals who have



become pregnant. Anemia of sprue often is associated with achlorhydria, although this does not occur by any means in many instances nor is it known, when it does happen that there is no hydrochloric acid in a sprue victim, whether or not this is an acquired or a constitutional tendency of the disease. The last conclusion the author draws is that while achlorhydria is the most tangible evidence of the constitutional background of pernicious anemia, it is by no means the sole one.

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## SURGERY

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UNDER THE CHARGE OF  
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**The Nerve Pathways in the Vomiting of Peritonitis.**—WALTON, MOORE, and GRAHAM (*Arch. Surg.*, 1931, 22, 829) say that the experiments here reported show that the vomiting of peritonitis is the result of the stimulation of afferent nerve endings located in the peritoneum. The emetic impulse thus initiated passes to the medullary center by way of sensory nerve fibers, which are included in both the vagal and sympathetic trunks. Section of these trunks prevents the occurrence of vomiting in peritonitis, although phrenic and other cerebrospinal nerve paths are left undisturbed. Since by sympathectomy alone, or by vagotomy alone, vomiting in peritonitis is not abolished, the afferent emetic impulse evidently traverses either pathway with equal facility. The consensus among anatomists seems to be that the parietal peritoneum is chiefly supplied by cerebrospinal somatic afferent nerves, whereas the visceral peritoneum receives its supply from the visceral afferent fibers that course in the vagal and sympathetic trunks. If this point of view is correct, the foregoing experiments indicate that it is the irritation of the visceral and not of the parietal peritoneum that gives origin to the vomiting in peritonitis.

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**Observations on Some Tendon Ruptures.**—PLATT (*Brit. Med. J.*, 1931, 366, 611) says that tendon ruptures may be divided into two main groups: the common rupture, produced by the sudden powerful overstretching of a muscle already in a state of contraction. Well-known examples of this type are disinsertion of the extensor tendons of the fingers and ruptures of the tendo-Achilles, rectus femoris and ligamentum patellæ. The second group comprises a less common and more insidious form of rupture—spontaneous rupture—seen in certain tendons which occupy a bony groove. In these circumstances the rupture is determined by a preëxisting adhesion of the tendon, which gradually becomes attenuated and ultimately snaps across in response to a comparatively trivial injury. The tendons most liable to rupture by this process of attrition are the extensor longus pollicis and the long head of the biceps. Tendon ruptures may also be classified according to the site of the tear which may take place (a) at the musculotendinous junction, (b) in the tendon itself, or (c) at the point of insertion. Tears in the neighborhood of the musculotendinous junction

are almost invariably incomplete and from a functional standpoint are equivalent to partial tears of the muscle belly—lesions which are usually included under the generic title of “strain.” This paper is mainly concerned with the problems of early diagnosis and operative repair in some of the more important complete ruptures. Early diagnosis and prompt treatment are greatly to be desired. Nine successful cases out of 10 cases of ruptured tendo-Achilles are recounted with “good function” in the remaining case. The best known of the spontaneous ruptures of tendon is that of the extensor longus pollicis, either associated or not with fracture of the lower end of the radius and usually following painful tenosynovitis. In such cases success in restoring function will not be attained unless the obliquity of the tendon is preserved.

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**The Use of Local Anesthesia in the Treatment of Fractures.**—HOSFORD (*Brit. J. Surg.*, 1931, 18, 546) claims that local anesthesia for setting fractures, when performed by injection 2 per cent novocain directly into the hematoma, which surrounds all parts of the fracture, is a safe and practicable procedure. Beyond the prick of the first hypodermic needle there should be no pain, except occasionally as the needle penetrates the periosteum and sometimes as the bruised soft parts are pressed upon during reduction. The latter, however, only occurs in fractures due to direct violence. Muscular relaxation should be as good as it is with general ether anesthesia and better than is usually obtained with nitrous oxid. Skiagrams should always be taken before injecting the novocain, so as to be certain as possible of getting the solution between or against the fragments, as failure to do this is almost invariably the cause of failure to bring about relief of pain and relaxation of muscle spasm, provided a freshly prepared 2 per cent solution of novocain is used.

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**Solitary Cysts of the Kidney.**—HIGGINS (*Ann. Surg.*, 1931, 93, 868) states that solitary cysts of the kidney are of more frequent occurrence than is apparent from the literature. A roentgenogram may reveal the presence of a cyst, especially if it arises from the lower pole of the kidney. Pre-operatively, a pyelogram may show a normal kidney. Functional tests may be normal and there may be no urinary symptoms. Conservative renal surgery is the indicated treatment for a solitary cyst either by dissection of the cyst away from the kidney tissue or by the removal of the cyst together with a small wedge-shaped portion of the pole of the kidney. This will then allow adequate approximation of the kidney tissue. Nephrectomy should be performed only in the presence of some coexisting renal pathologic condition, such as tumor, tuberculosis or calculi, if deemed advisable.

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**Fractional Gastric Analysis in 200 Cases of Duodenal Ulcer.**—BOCKIUS, GLASSMIRE and BANK (*Am. J. Surg.*, 1931, 12, 6) assert that the fasting residuum in many cases is characteristic. The quantity of the residuum is greater than normal, averaging 67 cc. It might be described as a thin, watery opalescent fluid often having a faint greenish or bluish tint. In 39 per cent of cases the residuum contained gross bile, a much greater incidence than in normal individuals. A post-

prandial hyperacidity was present in 84 per cent of cases. This percentage is slightly higher than any previous series reported. The finding of subnormal acidity is so infrequent in duodenal ulcer that one should hesitate before making a positive diagnosis of ulcer of the duodenum, if the acidity is subnormal. The review stresses the significance of delayed motility as determined by the fractional analysis in study of the patient with duodenal ulcer. The literature contains very little of value bearing on the effect of medical treatment in cases of duodenal ulcer as determined by the method under discussion. The incidence of cases having an ulcer relapse is recorded. The degree of gastric acidity seems to bear no relationship to the tendency to recurrence of symptoms. That is, relapses were not more frequent in cases showing extreme hyperacidity at the time of original examination than in cases with lesser grades of acidity. However, if repeated examinations show a tendency for the acidity to mount even higher, a recurrence should be anticipated. The majority of cases showing this tendency developed a return of symptoms. If, after four to six weeks of a strict hospital regimen, the fractional test shows a Grade II or greater delay, medical treatment is doomed to failure and surgery had better be advised.

**The Transmission of Syphilis by Blood Transfusion.**—POLAYES and LEDERER (*Am. J. Syph.*, 1931, 15, 72) state that the attention of the medical profession is called to the possibility of transmitting syphilis from donor to recipient or *vice versa* in the performance of blood transfusions. Ten cases of this nature reported in the literature since 1917 are reviewed and an additional case of an infant developing syphilis following a blood transfusion is described by the writer. Difficulties are encountered in determining whether or not the blood of a given donor is infectious. Cases are cited to prove that neither the absence of clinical signs nor a negative blood Wassermann reaction entirely excludes the possibilities of the existence of syphilis in the donor. It is urged that family donors should submit to the same rigid physical and serologic examination as professional donors, because in a large percentage of the cases family donors were responsible for the transmission of syphilis to the recipients.

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## THERAPEUTICS

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**Intramuscular Use of Liver Extract.**—It is now established that extracts of unusually small amounts of liver administered intravenously or intramuscularly will induce a remission in patients with pernicious

anemia. For patients who are very sick, or who require large amounts of the effective principle by mouth, or who are unable to take the extracts orally, STRAUSS, TAYLOR and CASTLE (*J. Am. Med. Assn.*, 1931, 97, 313) developed a product which is suitable for intramuscular use. The starting point in the preparation of this liver extract was the so-called "G fraction" of Cohn, Minot and their associates (Liver Extract No. 343 N. N. R.). An amount of this, derived from 10 kg. of liver, was poured into 1600 cc. of distilled water and the solution effected so far as possible by stirring and raising the mixture to the boiling point for five minutes. "During the warming of the solution, 6 cc. of tricresol was added and the mixture allowed to cool to room temperature. Seventy-five cubic centimeters of 5 normal sodium hydroxid was added to bring the solution to about pH 7.4 and 2.5 gm. of dihydrogen sodium phosphate dissolved in 10 cc. of distilled water was added to act as a buffer. The pH was checked. The volume was made up accurately to 2000 cc. and the solution allowed to stand in the icebox for 2 days. The supernatant liquid above the precipitate was removed by decantation and passed through a good grade of filter paper. The extract was then run through a Berkefeld filter and put up in 10-cc. amounts in glass vials with small rubber corks subsequently coated with collodion. Sterility tests were performed. Each vial contained the extract derived from 50 gm. of liver." The extract thus prepared was injected intramuscularly into each of 3 patients in amounts of 2 cc. derived from 10 gm. of liver. These patients felt better within 2 days; within 3 days an increase of the reticulocytes occurred, which reached its maximal level within 5 to 7 days. The red blood cell count increased rapidly. The intramuscular injections of liver extract caused no untoward reactions. The authors recommend that in severely ill patients a total of 4 cc. of the extract should be injected, preferably at two different sites. This should be followed by daily injections of 2 cc. The authors claim that the intramuscular administration of this liver extract may be particularly valuable in very sick patients, in patients who require unusually large doses of liver extract by mouth in order to induce remission and for improvement of the cord symptoms. The extract has also an advantage from an economic standpoint.

**Arsenic as a Therapeutic Agent in Chronic Myelogenous Leukemia.**  
—FORKNER and McNAIR SCOTT (*J. Am. Med. Assn.*, 1931, 97, 3) studied the effects of the administration of solution of potassium arsenite (Fowler's solution) in 10 cases of chronic myelogenous leukemia. Nine of these cases have shown entirely similar responses to the treatment. There has occurred a reduction of the white blood cell count to normal or nearly normal, an arrest of the progress of the anemia, a reduction in the size of the spleen and liver, and improvement in the patient's general condition. One patient failed to respond. The gradually increasing amounts of Fowler's solution administered varied up to about 50 minims daily. If indicated, the administration was temporarily discontinued. In general, it is advisable to administer the drug rather rapidly until the desired effect is produced or until intoxication occurs. The solution should then be discontinued for 4 to 6 days and resumed in small daily doses. The explanation of how the beneficial therapeutic changes are brought about is not discussed. The

results of treatment are in many respects analogous, it is claimed, to those produced by Roentgen rays and by radium. After complete withdrawal of the drug the white blood cell count remains low for about 3 weeks and then usually rises rapidly to or above the initial count. The administration of the drug should always be controlled by frequent blood examination. During the treatment the immature cells markedly decreased both absolutely and relatively. Frequently with the fall in the number of leukocytes, a relatively increase in the number of monocytes and basophilic granulocytes and an increase in the number of nucleated red corpuscles occurred. No essential change was observed in the number of blood platelets. Biopsy of the bone marrow suggested a return to red. The metabolic rate has been reduced to approximately normal levels. The authors claim that solution of potassium arsenite is of definite value in the palliative treatment of chronic myelogenous leukemia and perhaps can be used in conjunction with Roentgen therapy for the best sort of palliative treatment. The improvement can be maintained at least for a few months by the regular administration of small doses of the drug.

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## PEDIATRICS

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UNDER THE CHARGE OF

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**Poliomyelitis.**—CAMPBELL and MIRSKY (*Arch. Ped.*, 1931, 47, 543) discuss this disease very fully. They state that the following are the pathologic changes in the nervous system: Temporary meningitis due to mononuclear infiltration; edema with destruction of anterior horn cells which are poisoned by the toxin and strangled by the edema; general perivascular round cell infiltration; punctate hemorrhage, due to rupture of the pial vessels; shrinkage and lysis of anterior horn cells which become invaded by polymorphonuclear leukocytes; sclerosis in the late cases. The prophylactic treatment consists of the use of convalescent serum in doses of from 10 to 20 cc. at intervals of 4 to 6 weeks during the epidemic. In the preparalytic stage the treatment consists of the administration of convalescent poliomyelitis serum. This may be given intrathecally, intramuscularly or intravenously. At the onset of paralysis massive doses of convalescent poliomyelitis serum may be of some value. In the postparalytic stage the treatment is principally orthopedic care.

**Synostosis of Cranial Sutures.**—JACOBSEN (*Arch. Ped.*, 1931, 47, 556) reports 5 cases of synostosis of the cranial sutures which were discovered during a period of 6 months. In each of these cases the cranial deformities were the result of premature union of the sutures. In most of the cases the deformity was an oxycephaly, but in one a plagiocephaly developed. This deformity was extreme and offered an excellent opportunity at autopsy to study a severe case. In this case the brain was carefully studied for evidence of an abnormality which might

account for the closure of the sutures on the one side before those on the other side. No changes in the brain were found except those which seemed to be the result of the abnormal shape of the skull. Psychometric tests on these children indicated that the mentality was little, if at all, below that of normal children. In only one case was there much disturbance of vision, although it is possible that symptoms may develop in others later. Oxycephalic individuals as a rule have defective sight. The complaints are proptosis, headache, divergent strabismus, nystagmus and failure of vision. The most characteristic finding is optic neuritis. This is caused by increased intracranial pressure, small size of the optic foramina, upper deflection and stretching of the optic nerves as a result of bony deformity, and vascular conditions such as defective arterial supply or restriction of the venous return. The increased intracranial pressure was demonstrated by Roentgen ray pictures in all of the cases of this series. Various etiologic factors have been suggested as the cause of premature synostosis of the cranial sutures. Among these have been rickets, syphilis, fetal meningitis, pituitary disturbance and lymphatic polyglandular dystrophies. Heredity is thought to play little part in the etiology, but in this series 2 of the cases were brother and sister. The mother of these children was not oxycephalic but had unusually prominent eyes and a divergent strabismus. Two of her sisters were similarly affected. In these three sisters there must have been localized synostoses.

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**The Cure of Infantile Rickets with Tungsten-filament Radiation.**—GERSTENBERGER and HORESH (*J. Am. Med. Assn.*, 1931, 97, 766) used the CX Mazda lamp which is a 115-volt 500-watt tungsten filament housed in a Corex-D glass bulb of 1 mm. thickness, which has been frosted on the inside, and which transmits light waves down to 2800 Angström units. Three moderately severe rachitic infants, of whom 2 were negroes and 1 white, were cured, as shown by blood and Roentgen examinations, by daily 12-hour exposures to suberythematous doses of tungsten-filament radiation. The lamp was suspended in oxidized aluminum reflector from the ceiling of a room at a distance of 5½ feet above the bed level. This represented a total daily illuminating intensity of about 900 footcandle-hours or an average of illuminating intensity of 75 footcandles. The accuracy of the method of checking the rickets before exposure to the lighting scheme and the uniformity in the positive results obtained in each infant make the small number of 3 patients dependably accurate for the drawing of conclusions. The infants were dressed in shirt, diaper and booties, which left the head, neck and the greater part of the legs free for exposure. Goggles were used during the first few days, but were discarded without harm, because of the annoyance produced by the moisture collecting under them. No erythema was ever observed, although a mild but definite pigmentation gradually developed over the exposed areas. The negro infants perspired rather regularly, whereas the white infant showed sweating usually only after taking his bottle. This difference probably was due principally to increase of absorption and the decrease of reflection of the rays by the skin of the colored children, whose bodies responded as physical black bodies. No discomfort was noticed in the eyes, on the skin or on the mucous membranes. Infections of the upper respiratory tract that were

present when the observations were begun were not prevented from recurring, although they seemed to have become less severe. The results of the observations made, especially in view of the fact that curative dosage is larger than its preventive dose, indicate that the "dual-purpose lighting" as proposed by Luckiesh, probably will become feasible. A fourth infant was exposed front and back, at a distance of 80 cm. for  $1\frac{1}{2}$  hours to an intensity of illumination of 1200 foot-candle-hours produced by a portable unit with resultant complete healing within  $7\frac{1}{2}$  weeks of the moderately severe rickets as shown by blood and Roentgen examination.

**Pulmonary Tuberculosis in Children.**—LESTOCQUOY (*Médecine*, 1931, 12, 361) feels that it is the clinical observation of tuberculous children which furnishes the elements for the prognosis and the indications for the treatment. The weight curve, the improvement or the change in the general condition, and the temperature curve are the first and most important means of evaluation. The monthly taking of a Roentgenogram of the chest and its comparison with the preceding Roentgenograms must be considered as an absolutely necessary procedure. He considers no less important the use of a negatoscope. Monthly stomach lavages and the examination of the gastric contents for tubercle bacilli furnish new information of prognostic value. The new methods of blood examination and the speed of the erythrocyte sedimentation should be used. The author groups the indications for therapeutic pneumothorax under two headings. The diagnosis of the nature, site and extent of the lesions is based on knowledge of the family history, skin reaction and roentgenography and sputum examinations. The prognosis is based on weight curve, temperature curve and roentgenographic developments. It is absolutely necessary in children as well as in adults that the treatment be individualized.

## DERMATOLOGY AND SYPHILIS

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**The Contact or Patch Test in Dermatology.**—After outlining the simplicity of the method of performing a patch test, SULZBERGER and WISE (*Arch. Dermat. and Syph.*, 1931, 23, 519) stress its importance in the investigation of cases of acute eczematous dermatitis of uncertain etiology. It is of little value in cases of chronic lichenified eczema, neurodermitis, seborrheic dermatitis, urticaria and noneczematous drug eruptions. The chief value of the patch test is in the study of occupational dermatitis, in dermatitis venenata and in drug eruptions of ecze-

matous type—in other words, in all the more superficial acute or subacute eczematous reactions, whether from endogenous or exogenous causes. The authors caution against accepting as positive any substance which has not previously been investigated on normal skins to prove that it is not in itself a primary irritant. This is well illustrated in the case of soaps which, unless reduced to an emulsion sufficiently dilute to be injurious to normal skins, may give rise to false positive readings. Furthermore, a positive test does not *ipso facto* establish the relationship of the reacting substances to the dermatosis under investigation. A clear history of the opportunity for contact with the particular substance is essential. In addition, to be of diagnostic significance, the reaction must take the form of the dermatitis being investigated, that is, it must be an eczema of some kind. The authors reemphasize the question of polyvalent sensitizations, and state that a dermatitis so complicated may continue when only one of the causative factors is unearthed by patch testings. Furthermore, since spontaneous desensitization may occur, a negative patch test does not necessarily exclude the instrumentality of a substance which, from the history, seems a possible source of irritation. Subsequent retesting may establish its relationship to the eczematous reaction. The question is further complicated by the phenomena of local hypersensitiveness and immunity. For example, a local dermatitis may not be productive of generalized skin hypersensitiveness. Consequently the patch test may be negative to the known cause of the dermatitis. Despite these reservations, the authors conclude that the patch test is invaluable in the investigation of dermatitis of the eczematous type and should replace the scratch and intradermal methods in the study of such problems. In properly selected cases one may expect about a 30 per cent incidence of positive patch tests, and in this group such confirmatory evidence is invaluable from the therapeutic standpoint.

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**Reactions of the Skin Following the Intradermal Injection of Arsphenamin.**—MOORE, WOO, ROBINSON and GAY (*Arch. Dermat. and Syph.*, 1931, 23, 74) have carried out intradermal tests with arsphenamin products in four groups of persons: (1) 36 normal controls; (2) 61 patients with syphilis, most of whom had received therapeutic injections of arsphenamin without the occurrence of reactions of the dermatitis group; (3) 19 patients with allergic instability (hay fever); (4) 35 patients who had suffered from a postarsphenamin dermatitis. In about 60 per cent of normal persons a delayed reaction, "flare-up," developed at the site of intradermal injection after an incubation period of from 3 to 4 weeks. This has been interpreted as evidence of sensitization to arsphenamin. In a small proportion (44 per cent) of syphilitic patients under treatment similar reactions, which are less severe and extensive, developed which appeared earlier (in from 2 to 3 weeks) than in normal controls. This reduction in incidence and severity and the shortening of the incubation period were attributed to the desensitizing effect of previous or simultaneous intravenous administration of arsphenamin. In all except 1 of the 19 patients with hay fever tested much more violent and severe reactions developed, appearing earlier (in from 1 to 2 weeks) than in either of the control groups. This is interpreted, not as a sensitization to arsphenamin, but



as probably due to local autoinoculation of the sensitized patient with his own antigen (pollen) in an inflamed area (Auer's phenomenon). In the case of 35 patients with postarsphenamin dermatitis strongly positive reactions, appearing much earlier (in from 2 to 7 days) than in any of the other groups, occurred in 70 per cent of those who had had the exfoliative type of dermatitis, and in only 11 per cent of those who had other types of rashes. A negative skin test in postarsphenamin dermatitis does not indicate the absence of arsphenamin hypersensitiveness, in the opinion of the authors, since negatively reacting patients have often had repeated generalized rashes on attempts to administer therapeutic doses of these drugs.

## GYNECOLOGY AND OBSTETRICS

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**Irradiation of Cervical Cancer.**—There have been frequent changes of methods at The Mayo Clinic since the inception of irradiation treatment of cancer of the cervix in 1915 according to BOWING and FRICKE (*Minn. Medicine*, 1931, 14, 237). At present, intensive fractional dosage is employed, a massive dose being applied over a period of 2 to 3 weeks. The radium is used in 8 applications, being applied intracervically, interstitially, within the uterus and vaginally followed by 1, 2 or 3 courses of Roentgen treatment. The 50-mg. universal tube filtered through 1.5 mm. of monel metal or a tube containing 50 milluries of radon, enclosed in 0.5 mm. of silver and 1 mm. of brass is the usual radium applicator employed. The duration of each treatment is 12 to 14 hours. The entire length of the cervical canal and uterus is treated, applying 2 treatments to each 2.5 cm. of canal. In large cauliflower growths, radium in platinum needles is implanted, distributing the energy equally throughout the mass. The vaginal applications are made to the face of the cervix and in each fornix; the radium, besides its covering of monel metal, is shielded by 2 mm. of lead and 1 cm. of Para rubber. Treatments are given under direct inspection with the patient in the knee-chest position. Anesthesia is not required although a sedative is often given hypodermically. Seventy-five per cent of the early cases treated obtained a 5-year cure, while 61.53 per cent of the borderline, 21.49 per cent of the inoperable and 24.82 per cent of those with modified lesions obtained 5-year cures. The hospital mortality over a 10-year period has been 1 per cent. A study of 417 cases of cancer of the cervix treated at the State Institute for the Study of Malignant Disease at Buffalo by the combination of radium and Roentgen irradiation has been presented by SCHREINER and KRESS (*Am. J. Roentgen-*

ology, 1931, 25, 359). Using the Schmitz classification of the stage of the disease, they were able to obtain 5-year cures in 62.5 per cent in Group 1; 27.7 per cent in Group 2; 13.2 per cent in Group 3; 1.1 per cent in Group 4; and 6.5 per cent in Group 5. Combining Groups 1 and 2 which were the operable cases, 38.4 per cent have been clinically well over 5 years, while combining Groups 1, 2, and 3 in which at the time of admission it was thought possible to effect a cure, there were 37 out of 181 or 20.4 per cent clinically well over 5 years. These cases were all treated prior to 1926 and they believe that the improvement in technique since then should give better results in the cases treated since that time.

**Salpingography.**—The question has often been raised as to the ultimate fate of the oil which is injected into the Fallopian tubes in the performance of salpingography and the answer that is usually given is that it is gradually absorbed. Such an outcome does not always occur however, as evidenced by a case reported by NOVAK (*Zentralbl. f. Gyn.*, 1931, 55, 1449) in which lipiodol was found to be present in large amounts in closed tubes 15 months after it had been injected by way of the uterus for diagnostic purposes. The oil was found not only in the lumen of the tubes but upon microscopic examination it was seen to be present in the walls of the organs. Although no definite destructive changes were present, Novak feels that salpingography is by no means the harmless and safe method of examination which many investigators claim for it and that in most cases it would be much simpler and less dangerous to employ the tubal insufflation test in which only an absorbable gas is injected.

## OPHTHALMOLOGY

UNDER THE CHARGE OF

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**Hemorrhagic Retinal Lesions in Bacterial Endocarditis (Roth's Spots).**—DOHERTY and TRUBEK (*J. Am. Med. Assn.*, 1931, 97, 308) think that the characteristic retinal lesion of subacute bacterial endocarditis is a canoe-shaped hemorrhagic spot with a light central area situated in the most superficial portion of the nerve fiber layer. This type of hemorrhage appears suddenly and may remain only a few days. Quite similar hemorrhages were seen in severe pernicious anemia and were also observed immediately after a transfusion in a patient with a fever of unexplained origin. Round, elliptic or flame-shaped hemor-

rhagic spots without light centers may also be seen in subacute bacterial endocarditis but they are not pathognomonic. Lesions were found at some time in the retina of 11 of 25 patients with subacute bacterial endocarditis who were observed during their stay in the hospital. In 6, all or most of the hemorrhagic areas showed the typical white centers. In 4, the hemorrhages were atypical. In 1, round, white spots were present in the retina without hemorrhages. Histologically, these were found to be localized nodular swellings of the nerve fiber layer made up of a homogeneous mass simulating coagulated albuminous material without cellular infiltration. In 8 of the 11 cases blood cultures were positive for nonhemolytic streptococci, and in one other crushings of the valvular vegetations showed numerous streptococci. In 1, blood culture revealed a meningococcus. The retinal lesion is of diagnostic but not of prognostic value in subacute bacterial endocarditis, as it may appear and disappear in successive crops several months before death. In acute bacterial endocarditis a similar but more extensive retinal lesion may be seen as a late manifestation. There is edema of the retina with multiple discrete lesions, punctate elliptic hemorrhages with or without light center, or simply white spots. A histologic specimen from a case of acute bacterial endocarditis showed moderate edema of the retina with scanty polymorphonuclear infiltration of the nerve fiber layer, and localized lesions of the nerve fiber and ganglion cell layers consisting either of extravasated blood with neighboring edema and lymphocytic and polymorphonuclear infiltration or of polymorphonuclear infiltration alone. The choroid was relatively free of disease, containing only an occasional focal lymphocytic infiltration.

**Retinal Changes Due to Hypertension and Hypertonicity.**—GUIST (*Med. Klin.*, 1931, 27, 195) believes that because of the relative thinness of their walls the retinal veins show evidences of primary hypertension earlier than do the retinal arteries. When the blood pressure is elevated, before the arteries show any visible sclerosis, the thinner-walled vessels will become dilated and tortuous at the points of entrance of the blood from the arterial capillary into the venous system. This dilation will be evidenced by corkscrew tortuosity of the terminal vessels, especially in the macular region. By a study of the changes in the retinal vessels it is possible to differentiate the two main types of hypertension described by Pal, primary hypertonus and toxogenic hypertension. In primary hypertonus the arterial walls become thickened but the walls of the veins remain normal. This can be demonstrated histologically. The thickening occurs in the media of the arterial wall. Ophthalmoscopically, the small veins show corkscrew tortuosity while the veins in the neighborhood of the papilla appear normal, and pressure phenomena are seen at the arteriovenous crossings. In the early stages the vein is pushed back into the retina and appears narrowed on either side of the artery. When the arterial wall is definitely thickened, the vein in addition appears to be interrupted on either side of the artery. This marks an advanced stage of primary hypertonus. Advanced thickening of the arterial walls may also be evidenced by white strips accompanying the arteries throughout the retina. Choked disks may be present in this type of hypertension as an evidence of increased

intracranial pressure resulting from the hypertension. Intraocular hemorrhages may occur through rupture of a vein wall as a result of a sudden rise of pressure. In toxogenic hypertension the walls of both arteries and veins are thickened as evidenced by white strips accompanying both types of vessels in the retina. The terminal veins are not tortuous. The arteriovenous crossings are characterized by pressing forward of the artery toward the vitreous and narrowing and interruption of the vein on either side of the artery. The most typical form of toxogenic hypertension is lead poisoning. A similar picture is seen in secondary contracted kidney in which the vascular changes may be accompanied by retinitis. Histologically, the walls of arteries, veins and capillaries are found to be uniformly thickened in both retina and choroid. The changes in the walls of the retinal vessels remain as evidence of the hypertensive disease even if the blood pressure falls. The tortuosity of the veins resulting from venous stasis differs from that associated with hypertension in that it is seen in the veins around the disk and decreases in the smaller peripheral veins.

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**Lymphorrhagia Retinæ Traumatica.**—RADOS (*Arch. Ophthalm.*, 1931, 6, 93) reports a case of traumatic retinal lymphorrhagia following a fall from a horse with some compression of the thorax but without fracture of the skull or loss of consciousness. The patient complained of blurring of vision in the left eye shortly after the accident. Seven days later numerous white, shiny spots varying in size from one-half to 1 disk diameter were seen in the retina, encircling the disk and macula but leaving the macula free. The spots were situated in the inner layers of the retina, sometimes covering the vessels and arranged mainly along the veins. There were a number of small striate hemorrhagic areas around the disk and a preretinal hemorrhagic area nasal to the disk and one below the macula. The disk was clear. Folds were present in the retina between the disk and the macula. The retinal veins were markedly dilated and tortuous. These lesions cleared up in 4 weeks and the vision returned to normal. All the previously reported cases of this type followed head injuries, usually with fractures of the skull or severe concussion. Rados believes that the white patches are caused by the escape of fluid through small ruptures in the perilymphatic spaces around the retinal veins following a sudden increase in the pressure of the cerebrospinal fluid in the cranial cavity and the resultant forcing of the fluid into the vaginal spaces of the optic nerve with which the lymph spaces of the central vessels directly communicate. The prompt appearance of these patches (observed in 1 case 20 hours after the injury) and their relatively rapid disappearance indicate that the patches are due solely to the imbibition of fluid into the retina and not to secondary changes such as swelling of the axis cylinders and degeneration of the glial tissue. Cases in which white patches in the retina are associated with choked disks probably do not belong in this group. These cases are most often unilateral. While they usually follow head injuries, Rados believes that compression of the thorax or a sudden shortening of the spinal column can cause sufficient forcing of fluid into the cranial cavity to produce the retinal picture.

## OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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**Peritonsillar Abscesses.**—Endeavoring to define the anatomic relationship of peritonsillar abscesses, CANUYT (*Ann. d'otolaryngol.*, 1931, 1, 61) examined roentgenologically the localization of lipiodol injected into the faucial areas of cadavers and into previously aspirated peritonsillar abscess cavities *in vivo*. By these procedures it was learned that the abscesses occurred most frequently above and laterally to the tonsil—in the loose areolar tissue between the so-called tonsillar capsule and its pharyngeal bed. At times the lipiodol extended posteriorly, but never outwardly into the deeper cervical structures. For early diagnosis the author advocates exploratory paracentesis—by introducing a needle of wide caliber through the anterior pillar just laterally to the tonsil in the upper two-thirds for a distance of approximately 1.5 cm. Claims for efficacy of local anesthesia are made. Pus having been recovered on puncture, the anterior pillar is incised vertically from the upper pole of tonsil to the level of the lower third molar for a distance of 1.5 cm., keeping outside the capsule of the tonsil. If the pus is not encountered at this depth, the cavity is entered by a blunt instrument. Tonsillectomy during the acute stages of a quinsy is countenanced but not championed as a routined measure.

## RADIOLOGY

UNDER THE CHARGE OF

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**Necessity for Accurate Technique in Oral Cholecystography.**—Of the two methods of cholecystography, the oral method of administering the opaque dye is far more extensively employed. Yet it is widely assumed to be considerably less accurate than the intravenous method. KIRKLIN (*Am. J. Roent. and Rad. Therap.*, 1931, 25, 595), however, is convinced that this assumption has been derived from the experimental period of cholecystography when the methods of oral administration were diverse and highly imperfect, and that, if a rational and punctilious technique is employed, the diagnostic results following oral administration of the dye are fully as reliable as when it is given intravenously. Experience has shown that (1) the drug should be administered in sufficient quantity and freely absorbable form; (2) it should be so given

that it will not tend to excite nausea, vomiting or catharsis; (3) it should be taken into the stomach immediately after a full meal containing a minimal quantity of fats; (4) purgatives and medicaments that may affect the motility or absorbability of the bowel or the function of the gall bladder should be interdicted during and shortly before the examination. In compliance with these and other requirements, the author employs the following routine technique at the Mayo Clinic: Sodium tetraiodophenolphthalein is dispensed to the (adult) patient in a uniform dose of 4 gm. freshly dissolved in 30 cc. of distilled water. He is instructed to mix the solution with a glassful of grape juice, orange juice or carbonated water and to drink the mixture immediately after the evening meal at 6 P.M. It is urgently insisted that the meal be of substantial amount, reasonably free of butter, cream and other fats, and followed at once by the dye. Laxatives and other medicines are forbidden. At 7 A.M. on the morning of the test the patient takes a rectal injection of warm soap suds and continues until the enema returns clear. He is directed not to eat breakfast but is permitted to have water, black coffee or clear tea. Roentgenograms are made at 8 A.M., 10 A.M. and 2 P.M. Between the second and third sets of cholecystograms, the patient is directed to take with the noon meal a glassful of milk and cream or the equivalent in other fats if preferred. Items in the roentgenographic technique include a flat Potter-Bucky diaphragm high milliamperage, short exposure time, prone position of the patient in a comfortable posture, immobilization by a canvas strap drawn tightly over the back, and exposure in arrested respiration after deep expiration.

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**Intragastric Photography.**—THAL (*Radiological Review*, 1931, 5, 113) has for 2 years employed intragastric photography successfully in the demonstration of gastric lesions. Under fluoroscopic control a miniature camera is introduced into the stomach in the manner employed for passing a lavage tube, and the stomach is inflated with air. The camera carries eight small films, two of which are directed toward the lesser curvature, two each toward the anterior and posterior walls, and two toward the greater curvature. This practically covers an area of 5 or 6 inches longitudinally and includes the entire circumference of this section. The double views furnish stereoscopic prints on enlargement. They exhibit small ulcers and other minute lesions which may not be demonstrated by other means. The method can be used with rapidity, and with ease and safety to the patient. Its greatest value is when taken in conjunction with careful roentgenologic examination.

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**Biologic Sources of Radioactivity.**—In consonance with the findings of POLITZER, GURWITCH, CLARK and other investigators, WATTERS (*Arch. Phys. Therap., X-ray and Radium*, 1931 12, 272) finds that living plants and animals, including man, show a characteristic radioactive intensity. The radioactivity is so slight that instruments of great sensitivity are required, and Watters has devised an improved apparatus for this purpose. The hand, being the most accessible part of the human anatomy, was subjected to investigation, and was found to yield similar radiation measurements in all persons examined. The work was confined to normal persons, and it is not as yet known whether radia-

tion is altered by disease. Quantitatively the tongue gave off three times as much as the hand. About one-fourth of that emitted by the hand was given off by the cheek and forehead. Violent exercise seemingly produced a marked increase in the radiation output. Fatigue, however produced, increased the output. The radiation from fruits and vegetables when held between the cupped hands for 30 minutes increased to more than twice the normal, and was equal to that of the subject. Rays from the hand will penetrate paper, photographic film, and 1 mm. of aluminum. The rays are hindered by a vacuum and are influenced by magnets.

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**The Roentgenologic Demonstration of Polypoid Lesions and Polyposis of the Large Intestine.**—The commonly used opaque enema will often exhibit polypoid growths of the large bowel, but the results obtained by this method are not consistently reliable. A few years ago Fischer conceived the idea of employing air in combination with the enema and found it superior to ordinary procedures for demonstrating colonic lesions. WEBER (*Am. J. Roent. and Rad. Therap.*, 1931, 25, 577) has further modified Fischer's method with excellent results especially in exhibiting polyps. On the day before the examination the patient abstains from the evening meal and takes 2 ounces of castor oil. Next morning the bowel is cleansed by one or two plain enemas. At the laboratory an opaque enema with a consistence of heavy cream is administered, and the appearance of the bowel is studied fluoroscopically. The patient is then required to evacuate the enema as completely as possible, but a thin coating remains uniformly distributed over the intestinal mucosa. Then under fluoroscopic control the colon is inflated with a hand blower equipped with a self-retaining tip. Care is exercised not to overdistend any of the segments. After the bowel is inflated, the tip is removed, and stereoscopic roentgenograms are made. By these modifications, which comprise chiefly an almost complete evacuation of the enema and stereoscopic roentgenograms the internal topography of the bowel is exhibited throughout in minute detail, overlying loops of intestine can be studied separately in the stereoscopic view, and polypoid growths, however small, are readily discerned.

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**The Cancer Problem, Present and Future.**—Statistics, declares KRAEMER (*Am. J. Roentgen. and Rad. Therap.*, 1931, 25, 793) show that 1 person out of every 9 is afflicted with cancer at some time in his life. Seventy per cent of persons attacked by cancer die from its effects, and in the remaining 30 per cent practically all the cancers are found and treated at an early stage. Since 1916 the cancer death rate in the United States increased from 81.1 per 100,000 to 95.6 in 1927, or approximately 18 per cent. Search for the cause of cancer, for improvement in its diagnosis and for efficient treatment continues actively. In regard to therapy the author believes that, as an adjunct to surgery, Roentgen rays and radium, lead has a distinct place in the treatment of cancer, but should never be used alone as a major treatment, nor used with idea of breaking down a large tumor by causing thrombosis of its vessels.

## NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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**Diffuse Progressive Degeneration of the Gray Matter of the Cerebrum.**—ALPERE (*Arch. Neurol. and Psychiat.*, 1931, 15, 469) presents in great detail his gross and histopathologic studies of the cerebrum of a child who was apparently normal until the age of 3 months, when she suddenly began to cry a great deal, especially at night. She began to have attacks wherein she became completely stiff. Later she had convulsions of the entire body, during which her face was drawn to the left. Her physical examination showed slightly increased reflexes, underweight, unable to hold up her head, fixed pupils, pale optic nerves and a tendency to sleep much of the time. She seemed subnormal mentally. Laboratory examinations of the blood and spinal fluid were entirely negative. She was admitted to the hospital where she exhibited motor restlessness and a general intermittent rigidity of the musculature. On the second day in the hospital she exhibited a strabismus alternus and blindness. The ocular bulbs rotated downward. After cisternal puncture she collapsed, gradually recovered but then became progressively worse, went into a stupor and died. Gross examination of the brain revealed nothing other than a general softness which is found in a normal infant's brain. Microscopically the changes in the brain could be divided into two categories: (1) Structural changes and (2) developmental changes. The first type was represented by peculiar necrotic areas spread diffusely throughout the frontal, parietal and occipital regions and through the caudate, putamen, palladium, thalamus and pons. These were more pronounced in some places than in others, the whole producing a diffuse damage which tended to be more marked in some areas. The areas consisted of dilated capillaries, definitely increased in numbers, from which numerous capillary buds were springing, accompanied by a marked loss of ganglion cells; scattered among the capillaries in varying relations were astrocytes, microglia and fibroblasts. The latter were never frequent. In the younger areas the astrocytes were less numerous and the microglia relatively more numerous. In the older foci the astrocytes were markedly increased in number. Gitter cells were infrequent, and often they were absent. The striking feature in the cellular reaction within these areas was the predominant participation of the neuroglia, with the microglia assuming a relatively less important rôle even in the younger areas. The mesodermal elements were active in the multiplication of capillaries, and there was no diffuse deposit of connective tissue within the areas. The process was chiefly neuroglial with a minor participation of the mesodermal structures. In many regions there was a diffuse cell loss in the third lamina. The process was confined to the gray matter of



the cortex and subcortical areas, and in no instance did it spread over into the white substance. From this it was always sharply demarcated in areas involving the entire width of the cortex, or it was separated from the white substance, in some instances by a relatively intact lamina multiformis. There was demyelination of the cortex, striopallidum and thalamus. The entire brain showed evidences of developmental retardation. The entire subependymal region showed a layer of spongioblastic cells several layers thick and well demarcated from the underlying white matter. Scattered throughout the entire course of the frontal portion of the ventricle were foci of cells situated in the subependymal white matter or arranged around vessels. At the frontal pole of the ventricle was a large focus of giant cells. The entire white matter throughout the brain showed the presence of large numbers of immature ganglion cells, numerous astrocytes and a failure of oligodendroglia cells. The astrocytes were definitely hyperplastic—not typical adult fibrous astrocytes but immature juvenile forms with definite characteristics. In the white matter there was fat in abundance, spread diffusely or concentrated in foci. The axis cylinders were decreased in number in the white substance in many areas almost absent. In the parolfactory area there was a large focus of germinal cells, in the midst of which was an ependymal-lined pocket, and over the frontal cortex was a pial vessel with localized intimal proliferation. Many regions of the cortex showed a loss of cells in the lamina pyramidalis. The author compares his case with 2 others reported in literature, pointing out in great detail wherein they are similar and wherein they differ. He remarks that: "All 3 cases presented clinical pictures of Little's disease with subnormal mentality, hyperkinesias, choreoathetotic movements and epileptiform convulsions."

**Tumor of the Brain with Disturbance in Temperature Regulation.**—**STRAUSS and GLOBUS** (*Arch. Neurol. and Psychiat.*, 1931, 25, 3) report in detail 3 cases of tumor of the brain. They present an interesting review of the experimental work that has been done in attempting to localize the center of heat regulation and note that it is rather unfortunate that there are few clinical and pathologic observations to support these conceptions. They add that on the other hand ample clinical material indicates that the hypothalamus and adjacent parts of the diencephalon contain nuclei that regulate many of the vegetative functions, such as centers for carbohydrate metabolism, water elimination, protein metabolism, fat distribution, fat consumption, vasomotor function and the secretory activity of sweat and other glands. They further conclude, "If it is recognized that the production of heat is dependent on the carbohydrate, protein and fat metabolism, and that elimination of heat is procured through vasodilatation in the skin sweat secretion and elimination of fluids (urine and sweat), it becomes obvious that a heat regulating mechanism if it exists is likely to be located near centers that control functions essential for the maintenance of a balance between production and elimination of heat. This would seem to add weight to the belief that such a center has its location in or near the subthalamus." Each of the cases presented obvious difficult localizing problems and lacked convincing evidence of the presence of an expanding intracranial lesion. In Case 1 a diagnosis of cerebral

tumor was considered but the lack of objective signs and the misleading febrile course, with memory defect and somnolence as the only neurologic manifestations, made it almost impossible to reach a definite diagnosis. Necropsy revealed 3 tumor masses which were situated (1) in ependymal wall of anterior horn of lateral ventricle continuous with a mass infiltrating the septum pellucidum; (2) involving the body of the corpus callosum; (3) in right hypothalamic region directly above the optic tract infiltrating the lateral walls and almost the entire floor of the third ventricle but most prominent in the region of the tuber cinereum and massa intermedia. In Case 2 a cerebral lesion was suspected, based on the changes in personality, somnolence, headache, temporal anomia, slight right hemiparesis and increased deep reflexes on the right side. The presence of a febrile course was noted but its localizing value not recognized. Autopsy revealed 2 masses which were located respectively (1) in the third temporal convolution of the left hemisphere; (2) predominately in the right wall of the third ventricle occupying a large zone in the thalamus and subthalamus—the subependymal zone of the third ventricle of the left wall also being involved. Case 3 was diagnosed as a brain tumor probably located in the floor of the third ventricle. The diagnosis was based upon the changes in personality, slow progressive clinical course and a few objective signs. The significance of the febrile course was not recognized. Necropsy revealed a tumor of the third ventricle attached to or arising from the optic chiasm. In each of the 3 cases, a neoplasm in the subthalamic region with variable involvement of the hypothalamus and the thalamus was found. Because of the invasive character of the tumor, no limitations to distant nuclei could be established. The only interpretations drawn from the material was that "a lesion in the periventricular zone of the third ventricle and in the tuber cinereum caused a disturbance in the function of the heat regulating mechanism."

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## PATHOLOGY AND BACTERIOLOGY

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### The Effect In Vitro of Environment on the Virulence of B.C.G.—

There has been a continued discussion concerning the virulence of the B.C.G. as well as on the fixed character of the biologic properties of this organism. Calmette has stoutly maintained the innocuity of the B.C.G. for man and cattle. Others have found a varying virulence in experimental work with lower animals. It would appear that the attenuation of the organism may be maintained as long as it is grown on the bile-glycerin-potato medium. When, however, grown on other media and selection of colonies made, a virulent strain can be obtained

from the original culture. SASANO and MEDLAR (*Am. Rev. Tuberc.*, 1931, 23, 215) confirmed the findings of the avirulence of the B.C.G. when constantly grown on the bile medium. They found, however, that occasionally small lesions were present in the spleen and liver. They then undertook to observe the organism when placed on a different medium. For this purpose they used Souton's medium to which 10 per cent unheated rabbit serum was added. By a continued cultivation in this new environment they found that the organism showed virulence which increased with time and transplant. The same results were obtained in guinea pig and rabbit. From these results they conclude that it is possible to enhance the virulence of B.C.G. when grown in a suitable environment. Their method of demonstrating virulence differed from that of Petroff, who established dissociation of B.C.G. with the development of virulent colonies. These experiments indicate that the B.C.G. culture is not of the nature of a fixed virus.

**Chronic Typhoid Cholecystitis.**—MALLORY and LAWSON (*Am. J. Path.*, 1931, 7, 71) have made a study of the gross and microscopic appearance of the gall bladders of 7 typhoid carriers. All of these had common characteristics. The gall bladders were all within the normal limits of size. The walls were usually of normal thickness, though sometimes slightly thickened or thinned. The mucosa was relatively thickened in proportion to the other layers. There was no exudate or congestion of the serous surfaces. The content of the gall bladders was pale mucoid fluid and in all cases but one gall stones were present. Microscopically an inflammatory infiltration was present in every instance, often confined to the mucosa and always most marked there. The cells consisted of lymphocytes and plasma cells, the former predominating. The subepithelial capillaries were dilated and contained numerous polymorphonuclear leukocytes, and these were present in considerable numbers between the epithelial cells, apparently migrating to the lumen. Hyperplastic lymph nodules were frequently seen in the walls. Cultures of the bile showed *B. typhosus* in pure culture. These organisms could not be demonstrated in any of the layers of the wall. A review of 400 routine sections of chronic cholecystitis showed a similar lesion in 6.5 per cent of cases, while a review of the clinical histories showed that this picture had been found in 25 per cent of cases with positive histories and in only 4.9 per cent of cases with negative histories. The authors suggested that the lesion described was characteristic of chronic typhoidal cholecystitis but not pathognomonic of it, being a nonspecific reaction to persistent infection of the bile in contrast to the more usual type of chronic cholecystitis with sterile bile and persistent infection of the gall bladder wall.

**Renal Calcification and Bright's Disease.**—The diverse forms of calcification of the kidney being classified according to both topographic and pathogenic conceptions, PATRISSI (*Arch. di Patol. e Clin. Med.*, 1930, 10, 104) takes into particular consideration the calcareous metastases, of which he discusses the significance and causes especially in connection with the recent experimental results. Modern biochemical researches which tend to demonstrate the importance of metabolic disturbances, especially of calcium metabolism in relation to renal

dysfunction, have led the author to investigate systematically the existence of calcareous deposits in 148 kidneys, which were affected by various types of kidney lesions. Forty-one of these kidneys demonstrated the presence of calcification of varied extent, which from the morphologic point of view, were distributed in the following manner: (1) Calcareous crystals in cortical cysts, twice; (2) calcareous granules in hyaline glomeruli, three times; (3) calcareous deposits in glomeruli functioning although changed, three times; (4) calcareous deposits in the arterial walls, once; (5) calcareous casts in the lumina of the cortical or medullary tubules, thirty-five times. Calcareous deposits of the kidney were found with particular frequency in chronic glomerulonephritis (8 out of 17), especially in the extracapillary form and in tubular nephritis (18 out of 43); primitive scleroses follow in a decreasing proportion (14 out of 58); and acute and subacute glomerulonephritis (1 out of 10). They appear to be absent in all of the 20 cases of nephropathy other than Bright's disease (renal tuberculosis, etc.). Having made a résumé of the recent knowledge on the calcium metabolism of the blood and tissues, and on its mechanism of control, the author interprets the histologic findings obtained by the aid of the physiochemical findings. Having examined the reciprocal importance of the glomerulus and of the uriniferous tubule in the elimination and regulation of calcium, he concludes that the most significant endotubular calcification is the consequence of imperfect elimination of the calcium in the form of an unstable complex, arising from the tubular epithelium, and that for this reason it is more frequent in the field of tubular nephritis, which clinically presents hypocalcemia and albuminuria. In Bright's disease especially, the existence of calcareous casts in the uriniferous tubules would be, in consequence, symptomatic not only of a disturbance of calcium metabolism, but also of a condition of disease of the secreting tubular epithelium.

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**A Comparison of the Inclusion Bodies of Fowl-pox and Molluscum Contagiosum.**—In a comparative study, GOODPASTURE and WOODRUFF (*Am. J. Path.*, 1931, 7, 1) have found that the cytoplasmic inclusions of molluscum contagiosum could, like those of fowl-pox, be freed from the tissue by tryptic digestion. After digestion the molluscum bodies, unlike fowl-pox inclusions, were found to be sticky and gelatinous and therefore difficult of manipulation with microdissection apparatus. The gelatinous matrix of the molluscum bodies had a markedly granular appearance due to the presence in it of myriads of Lipschütz granules, minute coccoid structures  $0.25\ \mu$  in diameter. These granules were identical in size, shape and staining reaction with the Borrel bodies of fowl-pox and like them were resistant to the action of trypsin. Fowl-pox inclusions showed marked swelling when placed in distilled water, while those of molluscum showed little or no swelling under these conditions, due probably to differences in the permeability of their membranes. Trituration of the molluscum inclusions readily broke them up into the component Lipschütz granules. On the other hand, similar treatment of fowl-pox inclusions failed to disintegrate them so readily into Borrel bodies. The authors believed that this difference in the reaction of fowl-pox and molluscum inclusions to trituration might afford an explanation of the relatively greater filtrability of the latter.

Fowl-pox and molluscum contagiosum were apparently specific for fowls and man respectively since cross-inoculation experiments proved unsuccessful. Attempts to transfer molluscum to monkeys and other laboratory animals also failed.

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**Infectious Cirrhosis.**—From a study of 65 cases of "biliary cirrhosis" McMAHON (*Am. J. Path.*, 1931, 7, 77) has described the clinical and pathologic picture of uncomplicated infectious cirrhosis which was found in 5 cases and has contrasted it with that of obstructive cirrhosis. Infectious cirrhosis was found to be due to an infection within the terminal bile ducts which invaded the adjoining lobule, the picture being that of an acute inflammation within the portal areas. Infiltrations of polymorphonuclear leukocytes and endothelial cells were found in the surrounding portions of the liver lobules as well as in the bile ducts themselves. Later in the reaction endothelial cells predominated and healing took place by fibrosis accompanied by proliferation of bile duct epithelium. In the early stages the liver was normal in size; in the chronic and healing stages it was enlarged while the healed stage was characterized by a contraction of fibrous tissue so that the liver returned to about normal size. In long standing and healed cases of infectious cirrhosis the signs of a severe degree of obstruction to the portal circulation, *e. g.*, esophageal varices, large spleen and ascites were found—signs which were lacking in the cases of the obstructive type.

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## HYGIENE AND PUBLIC HEALTH

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UNDER THE CHARGE OF

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### Significance of Positive Wassermann and Kahn Reactions in Leprosy.

—In dealing with leprosy one frequently is confronted with the question whether a given case has syphilis as a complication. The diagnosis of syphilis in nonlepers is not always simple, but in lepers it is in many instances extremely difficult. The history obtained in many cases is unreliable; and due to the similarity of some of the manifestations of the two diseases, the diagnosis on clinical findings alone may be impossible. What significance, then, can be placed upon the usual serologic tests? BADGER (*U. S. Pub. Health Rep.*, 1931, 46, 957) undertook the present study to obtain, if possible, further evidence as to the significance of positive serum reactions in leprosy. The Wassermann and Kahn tests are made with the sera of all patients entering the Kalili Hospital, Leprosy Investigation Station, Honolulu, and this report is based on the findings of these tests with the sera of 207 patients over

10 years of age. There occurred an abnormally high incidence of positive serum reactions in the cases studied. The positive reactions occurred nearly twice as frequently among the females as the males. The positive reactions were more frequent among the patients under than those over 20 years of age. Positive reactions were three times as frequent among the lepers as among a control group. Definite changes in the serum reactions correlated with changes in the clinical manifestations of the leprosy were observed.

#### Natural Disappearance of Malaria in Certain Regions of Europe.—

HACKETT and MISSIROLI (*Am. J. Hyg.*, 1931, 13, 57) state that areas in which malaria has spontaneously disappeared in southern Europe are characterized by the production of *A. maculipennis* in vast numbers and by the fact that they are no longer even potentially malarious, so that the casual or continual introduction of gametocyte carriers does not reestablish the endemic. Such areas are usually well-defined zones in the heart of malarious regions and differ in this respect from that extensive borderland at the northern limit of malaria distribution from which benign tertian malaria seems to have been gradually receding in the course of the last century. The disappearance of malaria from regions of "anophelism without malaria" has been attributed to the development of an immunity to infection in the local anophelines; or to the elimination of gametocytes through the effective treatment or enhanced natural resistance of a prospering community; or to an effective interruption of the contact between anophelines and man. The authors have repeatedly shown, however, that anophelines from nonmalarious regions are infected by suitable carriers in the same proportion as those from malarious regions. There has never been reported a successful attempt to reduce gametocytes in a malarious population, by treatment or otherwise, to such a point that transmission can no longer take place in the presence of a sufficient number of anophelines. An illustration of this is the campaign at Torpè (Sardinia) where 3 years of intensive quininization have failed to reduce the high incidence of malaria. On the other hand, following an unusual invasion of anopheline mosquitoes, the rapid development of severe epidemics of malaria in communities where autochthonous malaria has not existed for years, or has never existed, shows that sources of infection are never absent in nonmalarious areas when these are located in a generally malarious region. An exact determination of the sources of blood meals of anophelines captured in Massarosa and many other typical examples of "anophelism without malaria" show that the attractiveness of domestic animals for *A. maculipennis* in such regions is at least fifty times that observed in the malarious regions studied, and that the consequent dissociation of *Anopheles* from man is a sufficient explanation of the cessation of malaria transmission. The causes of this dissociation have been studied experimentally in an isolated farmhouse in Massarosa. The results show that the type of shelter in which a food supply for *A. maculipennis* is available has little influence on its behavior, but that its movements and food preferences are largely determined by an instinctive attraction (tropism) toward the species of animal on which it habitually feeds. This attraction appears to be exerted through an odor of the animal or animals in question. It appears that *A. maculi-*

pennis show little tendency to return to the same quarters where they have previously obtained food, and that they are not immobilized for long by the presence of an abundant source of nutrition or diverted from an accustomed food supply by the comfort of an ideal shelter. In short, given a very large production of *A. maculipennis* with the presence of continuously stabled domestic animals in sufficient numbers to provide an unlimited food supply, there may be obtained in a given area, as a result of more prolific breeding over a period of years, a preponderant strain of zoöphilic mosquitoes which are attracted strongly by the odor of domestic animals but not by that of man. This preponderance will eventually reach a point where man is bitten so infrequently as to render the transmission of malaria virtually impossible.

**The Stillbirth Problem in the United States.**—STERLING (*Pub. Health Rep.*, 1931, 46, 207) describes this subject briefly and presents the following summary: In the United States the stillbirth problem is one of greater magnitude than that of neonatal death. While the decline in the neonatal death rate is slight, the stillbirth rate apparently shows no decline at all, the curve being practically a straight line. What effect, if any, more complete reporting of stillbirths would have on this curve cannot be estimated. Most prominent among the known causes of stillbirths are the complications of labor, syphilis and the toxemias of pregnancy. In the 7-year period from 1922 to 1928 the stillbirths from the toxemias of pregnancy have risen slightly, those from the complications of labor have fallen only very slightly, and those from syphilis do not appear to have changes significantly. For the prevention of stillbirths we must have better obstetrics and midwifery; more careful medical examinations during the last month of pregnancy; thorough treatment of the syphilitic pregnant woman; medical supervision during pregnancy; and more research into the toxemias of pregnancy and the fundamental causes underlying fetal death.

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ORIGINAL ARTICLES.

OBSERVATIONS ON THE ETIOLOGIC RELATIONSHIP OF  
ACHYLIA GASTRICA TO PERNICIOUS ANEMIA.

IV. A BIOLOGIC ASSAY OF THE GASTRIC SECRETION OF PATIENTS WITH PERNICIOUS ANEMIA HAVING FREE HYDROCHLORIC ACID AND THAT OF PATIENTS WITHOUT ANEMIA OR WITH HYPOCHROMIC ANEMIA HAVING NO FREE HYDROCHLORIC ACID, AND OF THE RÔLE OF INTESTINAL IMPERMEABILITY TO HEMATOPOIETIC SUBSTANCES IN PERNICIOUS ANEMIA.\*

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EXPERIMENTS have already been reported which in our opinion demonstrate the existence of an etiologic relationship between achylia gastrica and pernicious anemia, and define somewhat the nature of the mechanism involved in the production of the disease.<sup>1,2,3,4</sup> In the course of these observations it was found that the administration of either beef muscle or normal human gastric juice independently to suitable patients with Addisonian pernicious

\* The expenses of the present investigation were borne in part by grants from the J. K. Lilly gift to the Medical School of Harvard University.



anemia had no significant effect on blood formation. On the contrary, it was observed that if under appropriate conditions an opportunity for contact between these two substances was permitted, a remission was at once brought about quite as if liver had been administered. This hematopoietic effect was demonstrated to be due in all probability to an interaction between a protein or closely related substance in the beef muscle (extrinsic factor) and a product secreted by the normal human gastric mucosa (intrinsic factor). Because of the negative effect of feeding beef muscle alone to cases of pernicious anemia it was inferred that the intrinsic factor present in the normal human gastric juice was absent from the gastric juice and other digestive secretions of pernicious anemia patients. It was not demonstrable in normal human saliva or duodenal contents free of gastric juice.

Although these observations correlate perfectly with the well-known difference between the acid content of the stomach of normal individuals and that of the vast majority of cases of Addisonian pernicious anemia, it has already been pointed out that this difference in effectiveness cannot be directly related to the lack of acid alone.<sup>3</sup> The nature of the intrinsic factor in the normal human gastric juice has been sufficiently defined to preclude its identification with hydrochloric acid or with any of the common enzymes of the normal stomach.<sup>5</sup> The unknown factor is destroyed in 5 minutes by boiling, in  $\frac{1}{2}$  hour by a temperature of from 70° to 80° C., or in 3 days at 40° C. The intrinsic factor of the normal gastric juice interacts with the beef muscle at neutrality, and even though freed of pepsin and rennin by adsorption methods, the gastric juice is still effective. Furthermore, neither commercial pepsin, rennin, nor any of the enzymes present in the normal human duodenal contents free of gastric juice have been found able to carry out the essential reaction with beef muscle. From these observations it is apparent that the absence of hydrochloric acid or, indeed, of any of the common enzymes from the gastric juice of the pernicious anemia patient does not explain its inability to react specifically with beef muscle as does normal gastric juice.

There is, then, no theoretical objection to our hypothesis of the nature of pernicious anemia in the observation that certain patients with the blood picture of pernicious anemia have an apparently normal gastric contents.<sup>6,7,8,9</sup> On the other hand, there is not necessarily any contradiction to our hypothesis in the fact that certain patients showing no evidence of the blood picture of pernicious anemia have a total anacidity and sometimes a gastric content in no respect distinguishable by the usual clinical tests from that of Addisonian pernicious anemia.<sup>10,11,12</sup> Nevertheless, we have desired to clarify this situation, and from a study of these seemingly contradictory exceptions to add, if possible, to the already accumulated negative evidence positive support for our hypothesis.

At the moment there seems to be no way by which to determine the presence or absence of the intrinsic factor in gastric juice, except by actual trial of its effect after incubation with beef muscle upon a patient with Addisonian pernicious anemia. The apparently normal gastric juice of 2 patients with the blood picture of Addisonian pernicious anemia has, therefore, been so studied as well as the highly abnormal gastric contents of 4 patients with a complete anacidity, of whom 1 had no anemia and 3 hypochromic anemia subsequently responding to iron.

The cases used as test subjects in the studies reported in this paper and its predecessors were all patients with classical Addisonian pernicious anemia placed on diets containing no meat, liver or kidneys. During periods of daily administration of test preparations the absence of a significant increase of reticulocytes within 10 days was regarded as evidence of a lack of hematopoietic effect, while an appropriate increase within 10 days was considered a positive result. The use of the reticulocyte phenomenon in pernicious anemia has been fully discussed by Minot and his associates,<sup>13,14</sup> and we have already demonstrated its applicability to this particular problem.<sup>2,3,4</sup> The data given in Table 1 are for alternate days only during the administration of test preparations. No attempt is made to represent the changes of red blood cells and hemoglobin beyond the actual periods of test administration, since the reticulocyte curves in cases with less than 3 million r. b. c. per c.mm. give in the space of a few days far more definite information.

**Assay of the Apparently Normal Gastric Juice of 2 Patients With the Blood Picture of Pernicious Anemia Before, and of 1 of These Patients After Treatment With Liver Extract.** The first of these patients, Case 39,\* a man entered the hospital with a chronic irregular diarrhea (sprue) acquired in China. Despite his statement of some improvement 4 years ago on first taking  $\frac{1}{4}$  pound of liver daily, he had recently begun to lose strength, although continuing this therapy. His blood at entry showed 1.51 million r. b. c. per c.mm. and was in all ways typical of pernicious anemia. Gastric analysis, however, showed a normal amount of free hydrochloric acid and enzymes. Nevertheless, as a basis for planning experiments, it was assumed that this patient, like other cases of pernicious anemia, would respond typically to either the administration of the product of an effective interaction between beef muscle and normal gastric juice or at least to a sufficiently increased amount of the active principle of liver. On this assumption, possible explanations of this patient's anemia would be, according to our hypothesis, as follows:

(1) That the patient's diet had contained an insufficient amount of the extrinsic factor, already demonstrated to be present in beef muscle, to react with the intrinsic factor of the apparently normal gastric juice. (2) That although the interaction of the extrinsic and intrinsic factors occurred in this patient, he was unable, because of the diarrhea or associated loss of assimilation power of the intestinal tract, to absorb the results of that activity. (3) That although apparently normal, the gastric juice of this

\* For the details of the history and course of this and the other patients studied, see Appendix.

patient, like that of other cases of pernicious anemia, contained in reality none of the intrinsic factor shown to be present in the gastric juice of the normal individual.

The first of these possibilities was tested by giving to the patient each day for 10 days 200 gm. of nearly raw, finely ground beef muscle. The results of this therapy in Case 39, as shown in the first period of Table 1, testify to its entirely negative effect on reticulocyte formation. Since it was known from previous observations that 200 gm. of beef muscle contain a sufficient amount of the extrinsic factor to react effectively with as small an amount of normal gastric juice as 75 cc., and since gastric analysis showed an excellent secretion, the first possibility was considered to be excluded.

The second possibility, that of faulty absorption, was next examined by giving the patient in the next succeeding period of 10 days 150 gm. of raw liver daily. This dose of liver pulp has been shown to have approximately the same effect on cases of pernicious anemia as the interaction of 150 cc. of normal human gastric juice and 200 gm. of beef muscle.<sup>3</sup> The data given in the second period of Table 1 for this patient, Case 39, show a definite but moderate peak of reticulocytes of 7.8 per cent on the eighth day of the liver feeding from an initial level of 1.04 million r. b. c. per c.mm.\* The average response of reticulocytes to be anticipated under these circumstances, according to the data of Minot and his associates,<sup>13</sup> is about 16 per cent. It, therefore, became evident that this patient, although not as responsive to liver as most cases of pernicious anemia, was capable of reacting at least qualitatively in the typical manner, and thus the assumption originally made from the appearance of the blood picture seemed justified. This was further evidenced by the progressive clinical improvement and the increase of red blood cells under subsequent liver extract therapy.

Since absorption of the effective principle of liver had been shown to take place, at least to some extent, the third possibility, that the gastric juice of this patient though apparently normal was in reality deficient in respect to the intrinsic factor, seemed at once to be indicated. This was confirmed by actually trying the effect of incubating the gastric juice of this patient with beef muscle *in vitro* and then administering the resulting material by stomach tube to another pernicious anemia patient with the usual achylia gastrica. The technique of securing the gastric juice was in no way different from that employed in collecting the morning fasting secretion of normal individuals after the subcutaneous injection of histamin, and has already been fully described.<sup>3</sup> The collections were made daily during the first period of 10 days before liver therapy was applied, and the incubation of 75 cc. of the gastric juice with 200 gm. of beef muscle was carried out in the usual manner *in vitro* at pH 7 after a previous period of incubation of the beef muscle with 5 gm. of pepsin and sufficient hydrochloric acid to give the mixture a pH of 3. The essentially negative results of the daily administration of this material to Case 40 for 10 days may be seen from an inspection of Table 1. In contrast to this appears the obviously positive effect on reticulocyte production during the immediately succeeding period of 10 days when the only change in the technique was the substitution of the same amount of gastric juice obtained from a normal fasting individual for the gastric juice of Case 39.

The second patient of this type investigated, Case 41, a man, entered the hospital because of chronic diarrhea and anemia following operations resulting in multiple intestinal anastomoses. He had once taken for a brief period Liver Extract No. 343 (N. N. R.), derived from 300 gm. of liver, daily, with what he thought was some benefit; but he had not taken

\* For convenience in referring to the tables the red blood cell count of the second day of the second periods is taken as the initial figure for those periods.

any liver or liver extract for 4 months. His blood at entry showed 0.87 million r. b. c. per c.mm., and was in all ways typical of Addisonian pernicious anemia. The gastric juice, however, contained a normal amount of free hydrochloric acid and enzymes.

Again it was assumed, because of the blood picture, that the response of the bone marrow would resemble that of cases with a similar blood picture and achylia gastrica. The three possibilities as to the mechanism producing this type of anemia, referred to above, were considered and tested as in the observations on the first patient, Case 39. The daily administration of 200 gm. of beef muscle for a period of 10 days increased the reticulocyte percentage to 5.2 on the sixth day of the therapy without clinical improvement. (See Table 1.) Such a response without evidence of clinical improvement at an initial level of only 870 thousand r. b. c. per c.mm. can hardly be regarded as significant, particularly when compared to the peak of 27.1 per cent of reticulocytes on the eighth day of the immediately following 10-day period of daily administration of Liver Extract No. 343 (N. N. R.) derived from 300 gm. of liver. Again the intimation was that the gastric juice of this patient, despite its seemingly normal characteristics, contained little or none of the essential intrinsic factor. This was confirmed by the entirely negative effect of giving each day for 10 days a mixture of 75 cc. of the fasting gastric juice of this patient after the usual incubation with 200 gm. of beef muscle to a typical case of pernicious anemia, Case 42. It was thus impossible to demonstrate by two methods of experiment, shown by control observations to be adequate to the task, the presence of the essential intrinsic factor in the gastric secretions of these two patients.

*Although this defect contrasted with the demonstrable presence of free hydrochloric acid, pepsin and rennin by the usual tests is striking, it is nevertheless the condition already shown to exist in the classical cases of Addisonian pernicious anemia in relapse.<sup>2,3,4</sup>*

So far the evidence is that after adequate treatment with liver the characteristic lack of free hydrochloric acid of the stomach of nearly all patients with pernicious anemia persists.<sup>15</sup> However, a few cases have been found to recover the power to secrete hydrochloric acid in the stomach.<sup>16,17</sup> Shaw<sup>18</sup> has reported the case of a patient with pernicious anemia who, although previously lacking in free hydrochloric acid, was found after a spontaneous disappearance of the anemia to have free hydrochloric acid in the gastric contents. Although it is evident in the light of our observations on the nature of the intrinsic factor that the reappearance of the acid does not necessarily imply the return of the absent intrinsic factor, it seemed possible that such patients as Cases 39 and 41, both of whom had free hydrochloric acid in the gastric contents during relapse, might be more likely than the average patient to recover the ability to secrete the essential intrinsic factor.

For this reason a few days after a remission had been produced in Case 41 by the administration of liver extract the gastric juice, which since the remission had shown no change in its content of hydrochloric acid or pepsin, was incubated daily with 200 gm. of beef muscle and the resulting material administered to another untreated case of pernicious anemia, Case 48. (See Table 1.) A peak of 10 per cent of reticulocytes was produced on

the tenth day at an initial r. b. c. level of 1.92 million per c.mm. The fasting gastric juice of Case 41 was collected in the usual manner each morning after the subcutaneous injection of histamin and before the daily dose of Liver Extract No. 343 (N. N. R.), derived from 300 gm. of liver, was given to the patient. By this technique it was considered impossible for any significant quantity of the liver extract given during the previous day to remain in the stomach until the next morning. However, it seemed possible that liver extract might have been excreted in the fasting gastric juice of the patient and so itself have yielded activity otherwise clearly attributable to the mixture of gastric juice and beef muscle. In order to exclude this possibility, 150 cc. of the gastric juice of a normal subject was collected daily after histamin stimulation immediately before the daily administration of Liver Extract No. 343 (N. N. R.) derived from 600 gm. of liver. This particular gastric juice alone was given daily to a patient with pernicious anemia, Case 49, for 10 days without effect on blood formation. (See Table 1.) Subsequently, this patient, Case 49, showed a response of reticulocytes of 12 per cent on the eighth day at an initial r. b. c. level of 1.95 million per c.mm. when given daily Liver Extract No. 343 (N. N. R.) derived from 300 gm. of liver.

It is to be remembered also that we and others<sup>3,19</sup> have found no evidence of such an effect with the fasting gastric juice of the normal individual whose body presumably contains the active principle of liver extract in abundance. The renewed activity of the gastric juice of Case 41 could thus best be attributed to the presence of the essential intrinsic factor shown to have been absent from the gastric juice before remission was induced by liver extract.

**Assay of the Apparently Defective Gastric Juice of 1 Patient Without Anemia and of 3 Patients With Hypochromic Anemia.** The first of these patients, Case C, a man, was admitted to the hospital because of a neurologic condition. His blood was entirely normal with a r. b. c. count of 5.4 million per c.mm., a hemoglobin of 90 per cent (14 gm. per 100 cc.), a w. b. c. count of 7300 and a stained blood film with normal differential white blood cell count and platelets. The gastric analysis, however, showed a complete absence of a free hydrochloric acid and only a trace of pepsin. Indeed, the rate of secretion was very slow, even after the subcutaneous injection of histamin. Nevertheless, on the basis of our hypothesis, it was considered possible that this gastric juice contained the intrinsic factor since the patient had no obvious defect of blood formation. Accordingly, by prolonged daily intubation of the patient, enough gastric juice, containing a great deal of mucus, was obtained for a trial of 8 days, with a daily average of about 40 cc. of this material. Each day 200 gm. of beef muscle were incubated for 2 hours with 4 gm. of pepsin, 75 cc. of water and enough hydrochloric acid to give an acidity of pH 3. The liquefied mixture was then neutralized to pH 7, and to it the gastric juice of this patient was added just before an incubation period of 2 hours. The resulting product was administered daily by stomach tube to a typical case of Addisonian pernicious anemia, Case 46. The patient responded to this therapy with a production of reticulocytes of 12.8 per cent at an initial r. b. c. level of 1.11 million per c.mm. on the tenth day of the observation, as shown in the first period of Table 1. Nor did the substitution of identical amounts of normal human gastric juice for the highly abnormal secretion of this patient, under similar conditions of incubation and administration, produce a second rise of reticulocytes in the succeeding period of 10 days.

Obviously the meager and apparently abnormal gastric secretions of this patient, Case C, obtained under circumstances identical with those employed in the collection of normal gastric juice, also contained the intrinsic factor. It became, then, possible to see how, without contradiction to our conception of the nature of pernicious anemia, this patient could potentially maintain a normal blood.

The next 3 cases studied, A, B and D, all women, did not have normal bloods. They showed, on gastric analysis, a lack of acid and enzymes quite similar to that encountered in Addisonian pernicious anemia. Yet the anemia was patently not of that variety. The salient characteristic was a marked relative reduction of the hemoglobin in respect to the number of red blood cells. Cases A and B in general corresponded to Faber's description of chronic chlorosis,<sup>10</sup> complicated by poor diets and some blood loss. Case D apparently suffered from chlorotic anemia of pregnancy, described by one of us,<sup>20</sup> and shown to respond readily to iron. Observations made by Mettier and Minot<sup>21</sup> have shown that similar patients will not ordinarily respond to extracts of liver effective in pernicious anemia, and these workers have also shown, with others,<sup>22,23</sup> the marked effect of large doses of iron in creating prompt reticulocyte responses, increases of red blood cells and hemoglobin and clinical improvement in such patients. These 3 cases were no exception, and either subsequently to or during the collection of their gastric juice for use in the observations to be described, showed typical responses to the oral administration of iron.

On the other hand, as will be seen from an inspection of the data for 3 patients with pernicious anemia, Cases 44, 45 and 47, given in Table 1, the apparently defective gastric juice of each of the 3 patients suffering from a hypochromic type of anemia, Cases A, B and D, was able to react successfully with beef muscle. During the first period of the observations on Case 44, 50 cc. of the gastric juice of Case A, when incubated daily with 200 gm. of beef muscle, and given under the conditions described for Case 46, effected a production of reticulocytes of 10.6 per cent on the eighth day of the therapy at an initial level of 1.82 million r. b. c. per c.mm. Similarly, 75 cc. of the gastric juice of Case B, although incubated and administered daily for only 7 days with 200 gm. of beef muscle, produced a response of 18 per cent of reticulocytes on the tenth day of observation of Case 45 at an initial r. b. c. level of 1.59 million per c.mm. Again, the daily incubation of 75 cc. of gastric juice from Case D with 200 gm. of beef muscle gave, on administration to Case 47, a peak of 9.6 per cent of reticulocytes at an initial level of 1.52 million r. b. c. per c.mm. on the eighth day of the therapy. It is therefore apparent that the gastric secretions of Cases A, B and D contained the intrinsic factor. However, observations made on these test patients, Cases 44, 45 and 47, in the period of 10 days

immediately following suggest that the concentration of the intrinsic factor was not equal in all of them to that of the normal human gastric juice. In the observations on Cases 44 and 47 secondary rises of reticulocytes of 12.6 and 7.8 per cent occurred respectively in response to the daily incubation of normal human gastric juice equivalent in amount to the quantity of the secretions of Cases A and D used during the immediately preceding periods. This phenomenon indicates clearly a greater potency of the normal gastric juice than of the juice of 2 of these 3 patients with hypochromic anemia.<sup>3,13</sup> However, it is interesting that the absence of a secondary rise of reticulocytes in Case 45 indicates no greater potency of the normal human gastric juice than of that derived from Case B, who, like all 4 of the patients of this group, had no free hydrochloric acid in the gastric contents. The properties of the gastric juice of the 6 patients studied, as described above, are summarized in Table 2.

**The Factor of Intestinal Impermeability.** The many instances reported in the literature of chronic diarrhea, partial obstructions or short circuits of the intestines associated with pernicious anemia<sup>8,24</sup> originally suggested to us the third possible mechanism of deficiency, namely, difficulty in the assimilation or further metabolism of the hematopoietic substance formed by the interaction of the intrinsic and extrinsic factors.<sup>4</sup> This explanation of the mechanism of the deficiency in the reported cases of this type appeared to be reasonable from the fact that in certain of them the gastric contents was stated to contain free hydrochloric acid.<sup>8,9</sup> The 2 cases reported in this paper as having a blood picture of pernicious anemia with an apparently normal gastric contents, Cases 39 and 41, seemingly fall into this clinical category. As did many of the reported cases, these 2 individuals suffered from persistent irregular diarrhea; in Case 39 associated with sprue and in Case 41 following repeated operations on the intestines. The effect of diarrhea in preventing the normal assimilation of liquids and food is well known. It thus originally seemed possible that chronic dysfunction of the bowel of both cases, indicated or induced by diarrhea, might have resulted in a disturbance of its absorptive capacity; a reduction of the absorbing surface was undoubtedly caused by the multiple operations in Case 41. These facts offered obvious grounds for a consideration of the possibility of defective absorption as the sole mechanism of the deficiency both in those cases already reported in the literature and in these 2 patients. Nevertheless, in these 2 particular patients before treatment clear evidence of a lack of the intrinsic factor of the gastric juice was obtained, and they were thus shown in that respect to be no different from the cases with achylia gastrica already studied.

However, it cannot be assumed from this that defective assimilation was not involved in certain of the other reported cases, or to

TABLE 1.—DIFFERENTIATION OF TYPES OF ACHYLIA ON BASIS OF INTRINSIC FACTOR.

## First Periods.

Daily administration of various substances as indicated below.

Days of treatment.	Beef muscle, 200 gm.	Beef muscle incubated with g. j. Case 39.	Beef muscle incubated with g. j. of Case 41.		Normal g. j. man given L. E. No. 343 (600 gm.).	Beef muscle incubated with g. j. Case A.†	Beef muscle incubated with g. j. Case B.‡	Beef muscle incubated with g. j. Case C.§	Beef muscle incubated with g. j. Case D.
			†Before remission.	†After remission.					
	Case 39.*	Case 40.	Case 41.**	Case 42.	Case 43.	Case 44.	Case 45.	Case 46.	Case 47.
	R.B.C. Ret. %	R.B.C. Ret. %	R.B.C. Ret. %	R.B.C. Ret. %	R.B.C. Ret. %	R.B.C. Ret. %	R.B.C. Ret. %	R.B.C. Ret. %	R.B.C. Ret. %
0 . .	1.65 0.8	1.05 0.6	0.87 0.2	0.97 1.4	2.05 0.4	1.82 2.2	1.59 2.4	1.11 0.0	1.52 1.6
2 . .	1.32 0.2	1.07 0.8	0.89 1.6	1.25 5.3	2.34 0.1	1.64 2.8	1.45 1.6	1.35 0.6	1.37 1.0
4 . .	1.68 1.4	0.87 0.6	0.93 1.4	1.22 1.2	2.54 0.1	1.84 3.8	1.18 2.6	1.45 1.4	1.62 1.4
6 . .	1.52 0.6	0.91 2.1	0.86 5.2	1.33 0.6	2.18 0.1	1.60 4.4	1.46 7.2	1.19 6.8	1.44 3.8
8 . .	1.45 1.2	0.97 1.5	0.89 3.4	1.32 0.8	1.92 0.1	1.86 10.6	1.51 14.6	1.38 8.2	1.35 9.6
10 . .	1.28 0.2	.. ..	.. ..	1.28 1.0	2.01 0.6	1.87 8.0	1.44 18.0	1.54 12.8	1.77 7.2

## Second Periods.

Daily administration of various substances as indicated below.

	Raw liver, 150 gm.	Beef muscle incubated with normal gastric juice.	Liver Ext. No. 343 (300 gm.). †			Liver Ext. No. 343 (300 gm.).	Beef muscle incubated with same amounts of normal gastric juice as in first periods.																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																												
2 .	1.04	1.2	0.79	2.8	0.85	3.8	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..

\*Case 39: Chronic tropical sprue with blood typical of pernicious anemia. Free HCl and enzymes present in gastric juice.

\*\* Case 41: Multiple intestinal anastomoses, blood typical of pernicious anemia. Free HCl and enzymes present in gastric juice.

† Remission induced by Liver Extract No. 343.

‡ Cases A and B: Chronic chlorosis with absent HCl and enzymes. Subsequent response to iron.

§ Case C: Idiopathic achylia without anemia. Absent HCl and enzymes.

|| Case D: Chlorotic anemia of pregnancy with absent HCl and enzymes. Subsequent response to iron.



a certain extent in Cases 39 and 41. Indeed, from the original observations on these 2 patients suggestive evidence of difficulty with the assimilation of the active principle of liver extract was obtained. Case 39 showed less than the normal response of reticulocytes, yielding only 7.8 instead of a theoretical 16 per cent of reticulocytes at an initial level of 1.04 million r. b. c. per c.mm. from the daily ingestion of 150 gm. of raw liver.<sup>13</sup> Although it is possible that the effect of the previous daily ingestion of  $\frac{1}{4}$  pound of liver, which was discontinued only 10 days before this observation, was responsible for the relatively slight increase of reticulocytes, this seems unlikely since the patient became progressively more anemic while on the former régime. Furthermore, both Cases 39 and 41 subsequently showed an unusually slow increase of red blood cells in response to large doses of liver extract, although the diarrhea was well controlled by opiates and there was no evidence of infection or marked arteriosclerosis. It therefore seemed probable that in

TABLE 2.—PROPERTIES OF GASTRIC JUICE ASSAYED FOR INTRINSIC FACTOR.

Case No.	Diagnosis.	Free HCl (N/10 HCl/100 cc.).	Pepsin.	Rennin.	Lipase.	Intrinsic factor.
39 . .	Normal	50	15	100-200	1-2	+
41 . .	P.A. (sprue)	10-70	17	66-333	2	0
41 . .	P.A. (intestinal)	52-83	15	110-166	...	0
C . .	Comb. sys. dis.	0	2.7	...	...	+
A . .	Chr. chlorosis	0	1	1-2	0	+
B . .	Chr. chlorosis	0	4	1-2	0	+
D . .	Chr. chlorosis	0	6	...	...	+

addition to the absence of the intrinsic factor from the superficially normal gastric juice of these 2 patients, there was also a defect of absorptive power which would have made difficult the assimilation of the hematopoietic substance had it been formed in the stomach.

The existence of intestinal impermeability to the hematopoietic products of gastric activity originally suggested by us<sup>4</sup> as having bearing on the etiology of certain cases of pernicious anemia appears even more plausible from the work of Gänsslen.<sup>25</sup> He first showed the remarkably increased effectiveness of the active principle of liver when given intramuscularly instead of by mouth. Schilling<sup>26</sup> has confirmed his observations, and his work corroborates the suggestion of Cohn, McMeekin and Minot,<sup>27</sup> that intestinal impermeability to the active principle may account for certain of the so-called "liver resistant" cases of pernicious anemia. Our studies of the active principle of the gastric mucosa have shown it to have entirely different properties from the active principle of liver, and in all probability to be identical with the hematopoietic product of the interaction of the extrinsic and intrinsic factors of normal human

gastric digestion.<sup>3</sup> Recently Ederle, Kriech and Gänsslen<sup>28</sup> have obtained satisfactory results with the daily intramuscular administration of an extract derived from 4 gm. of gastric mucosa in contrast to the usual necessary oral dosage of 150 or more grams daily. Independently of these workers we have shown that extract derived from 100 gm. of liver when intravenously administered will produce reticulocyte responses ordinarily equalled only by the oral administration of extract derived from 1500 to 3000 gm. of liver.<sup>29</sup> To what extent this difference involves a normal physiologic factor is unknown, but our own preliminary observations with intravenously

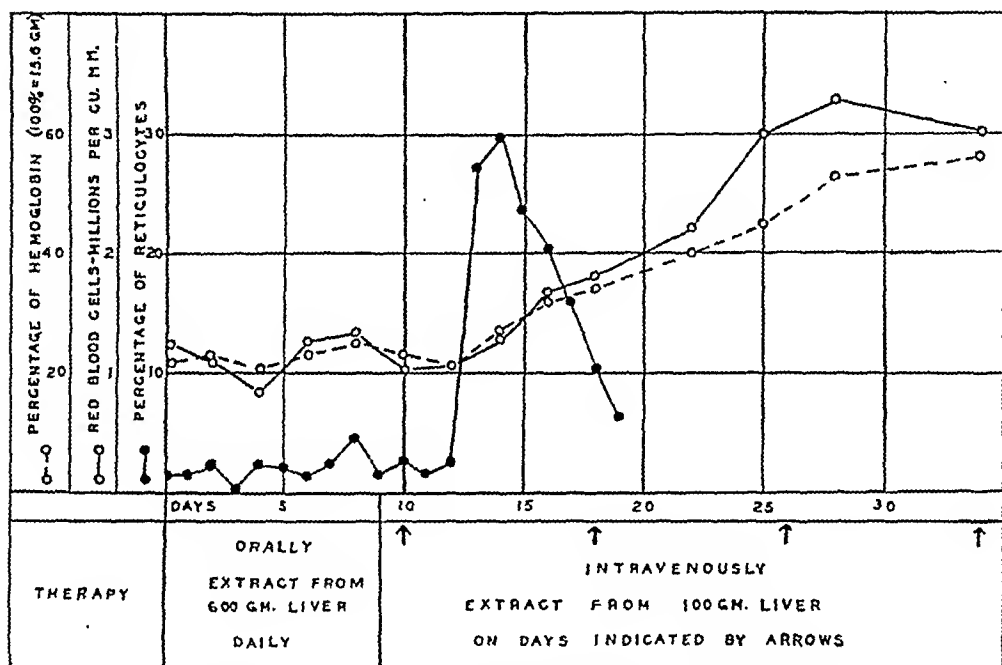


FIG. 1.—Intestinal impermeability to liver extract as illustrated by observations on a patient with pernicious anemia, Case 41.

Daily oral administration of potent liver extract derived from 600 gm. of liver was without effect on blood formation. A single intravenous injection of extract derived from 100 gm. of liver then produced a peak of 29.8 per cent of reticulocytes on the fifth day from an initial r. b. c. level of 1 million per c.mm.

administered liver extract make it evident that the effectiveness of the utilization of orally administered liver extract is a variable condition among cases of established pernicious anemia. Specifically, in Case 39, a year after the original remission described above, potent extract from 600 gm. of liver, given daily by mouth, was not sufficient to maintain a constant blood level of a little over 1 million r. b. c. per c.mm. Nevertheless, a single intravenous injection of extract derived from 100 gm. of liver produced a reticulocyte response of 29.8 per cent on the fifth day after the injection at an initial r. b. c. level of 1 million per c.mm. and a gain of almost 1 million r. b. c. per c.mm. within a week. (Fig. 1.) Since the effect of the

hematopoietic product of the interaction of the extrinsic and intrinsic factors closely resembles that of the active principle of liver, it is a reasonable assumption that the absorption of the former might be similarly embarrassed in certain cases of pernicious anemia. At some stage in the development of the disease this defect might limit the subsequent absorption of the hematopoietic product of the interaction between the extrinsic and any intrinsic factor present in the stomach of the patient.

**Discussion.** It may be considered that because of the relatively small number of patients forming the basis of the observations reported in this paper, little discussion of the results is possible. It should be noted, however, that the methods employed have been subjected to severe test over a period of years and that the control observations essential to the interpretation of the present experiments are based on the previous study of many patients.<sup>2,3,4,5</sup> Two of the observations reported in this paper were made upon patients, Cases 39 and 41, who had the blood picture of pernicious anemia but an apparently normal gastric juice. The observations showed that the gastric juice of these 2 patients, as of those with achylia gastrica, was defective in respect to the intrinsic factor found in the gastric juice of the normal individual. Since we have shown that the properties of the intrinsic factor are not those of hydrochloric acid or of pepsin or rennin, and that its specific activity with beef muscle cannot be replaced by any of those substances alone or in combination,<sup>5</sup> it is evident that no exception to our former observations on the etiology of pernicious anemia with achylia gastrica is offered by these cases with an apparently normal gastric juice.

On the other hand, it is not necessary to suppose that because the vast majority of cases of pernicious anemia show a gastric anacidity, a lack of acid is always evidence of an absence of the intrinsic factor which we believe to be the specific defect in pernicious anemia. This point is made very clear by the observations on the gastric juice of 4 patients, Cases A, B, C and D, who plainly did not have pernicious anemia but whose gastric contents contained no free hydrochloric acid even after the subcutaneous injection of histamin. The apparently abnormal gastric juice of these patients, indistinguishable by tests for acid or enzymes from that of many cases of pernicious anemia, nevertheless contained sufficient of the intrinsic factor to react positively with beef muscle. Indeed, the gastric juice of Cases B and C was not demonstrated to contain less of the essential intrinsic factor than similar quantities of normal human gastric juice. Case C had no anemia and thus, perhaps, corresponds to a certain number of normal individuals who have been found to have no acid in the gastric contents.<sup>30,31</sup> Cases A, B and D had hypochromic anemia in association with which gastric anacidity is frequently found.<sup>12,20</sup> Nevertheless, each had a gastric content potentially able to carry out the necessary reaction with

beef muscle to form the substance capable of relieving typical cases of pernicious anemia. For that reason we believe that they themselves showed no evidence of pernicious anemia despite the superficial resemblance of their gastric juice to that of cases of Addisonian pernicious anemia.

We have already discussed in the light of our earlier observations the ways in which a deficiency of the effective principle might theoretically be brought about and so condition certain individuals for pernicious anemia. In brief, it is obvious that an absence of one or both of the factors of the specific reaction or an inability of the body to use the product of their interaction might produce in different ways the same final defect. The aversion of many patients with pernicious anemia to meat for long periods before the development of the disease<sup>32</sup> suggests that their diet may have been partially or wholly lacking in the extrinsic factor shown to occur in beef muscle. The absence of the intrinsic factor from the gastric contents of pernicious anemia patients with achylia gastrica has already been inferred from the negative effect of feeding beef muscle alone to these patients, in experiments reported in the previous papers of this series.<sup>2,3,4</sup> Similar observations on Cases 39 and 41 further corroborated our already extensive negative evidence for that inference. Positive confirmation by direct experiment has, however, now been obtained from observations of the negative effect of incubating the apparently normal gastric contents of these 2 pernicious anemia patients with beef muscle *in vitro*. *Thus far, then, all the cases of pernicious anemia in relapse which have been examined by us have failed to show the intrinsic factor no matter what was the apparent condition of their gastric juice.*

It is, of course, not necessarily certain that the mechanism lacking at one time in a given patient is lacking at all times. A few days after a remission had been produced in Case 41 by the administration of liver extract the gastric juice of this patient was again tested for the presence of the intrinsic factor. In contrast to the negative effect obtained with the gastric juice secreted before the remission, the gastric juice obtained thereafter was found to react positively with beef muscle. (Table 1.) It is therefore probable that after remission the gastric juice of this patient, Case 41, contained the intrinsic factor as does the gastric juice of normal individuals, and therefore reacted positively with the beef muscle in a similar way. A recovery of the ability to secrete free hydrochloric acid has been observed in a few patients with pernicious anemia after treatment with liver.<sup>16,17</sup> Bloomfield and Pollard<sup>33</sup> have reported an improvement in the gastric secretion of a case of sprue after treatment, and Chang, Yang and Keefer<sup>34</sup> have observed an increase in the amount of hydrochloric acid secreted by certain cases of "secondary" anemia after treatment was instituted. Of course, in the light of our observations the reappearance of hydro-

chloric acid in the gastric secretions does not necessarily indicate the recrudescence of the essential intrinsic factor, but it does demonstrate an improvement of a function which is frequently lost in association with loss of the power to secrete the intrinsic factor. On the other hand, the usual failure of hydrochloric acid to reappear in the stomach of the case of pernicious anemia which has been treated *does not exclude* the possibility of an undetected improvement of the capacity of the stomach to secrete the *essential* intrinsic factor.

By the experiments reported above, an adequate criterion has been applied for the first time to the determination of the presence or absence of the intrinsic factor in the gastric juice of human beings, and so in our opinion a true measure taken of their immediate predisposition to pernicious anemia. The essential intrinsic factor, with or without a lack of free hydrochloric acid, has been found to be absent from the gastric contents of all patients with pernicious anemia in relapse so far examined and to be present in the similarly acid- and enzyme-free gastric contents of an otherwise normal individual, Case C, and of 3 patients with hypochromic anemia, Cases A, B and D. (Table 1.) There is, then, no paradox in the fact that a lack of free hydrochloric acid has been reported in normal young adults.<sup>30</sup> Nor is the fact that there may be an absence of free hydrochloric acid from the gastric juice of certain pernicious anemia patients for several years before the appearance of the anemia<sup>35</sup> inconsistent with our hypothesis. Moreover, as there seems to be a certain degree of correlation between a lack of the intrinsic factor and of free hydrochloric acid, and as gastric anacidity in normal individuals has been shown to occur with increasing frequency with advancing years,<sup>36</sup> we can perhaps now understand why the age incidence of pernicious anemia should be late rather than early in life. It is thus evident that the ability of the individual to carry out the specific reaction between the extrinsic and the intrinsic factors might decline with a progressive loss of the intrinsic factor over a period of years, with no obvious change in the ordinary clinical chemistry of the gastric contents.

Since gastric anacidity does not necessarily indicate a lack of the specific intrinsic factor and is commonly found in cases of idiopathic hypochromic anemia, it is now not difficult to understand the association of this type of anemia with pernicious anemia in those families known to show a high incidence of achlorhydria among their members,<sup>37,38</sup> some of whom may even show no evidence of faulty blood formation of any kind. Indeed, all these possibilities may even be successively represented in the history of a single individual, who may first show no anemia, secondly, an anemia of the hypochromic variety and, finally, a true pernicious anemia.<sup>39</sup> In the light of our observations such a sequence of events could be interpreted most simply on the basis that the pernicious type of anemia did not develop until the essential intrinsic factor had become

sufficiently diminished. For this to occur no change in the degree of achlorhydria need, of course, be manifest, since in the totally anacid gastric juice of Cases B and C a normal amount of the essential intrinsic factor was demonstrable, in Cases A and D a reduced amount was found, and in the typical cases of pernicious anemia none. *It therefore follows that unless a specific test is made it cannot be positively known whether the intrinsic factor is present or absent in any individual at any time no matter what is the condition of the gastric juice in other respects.*

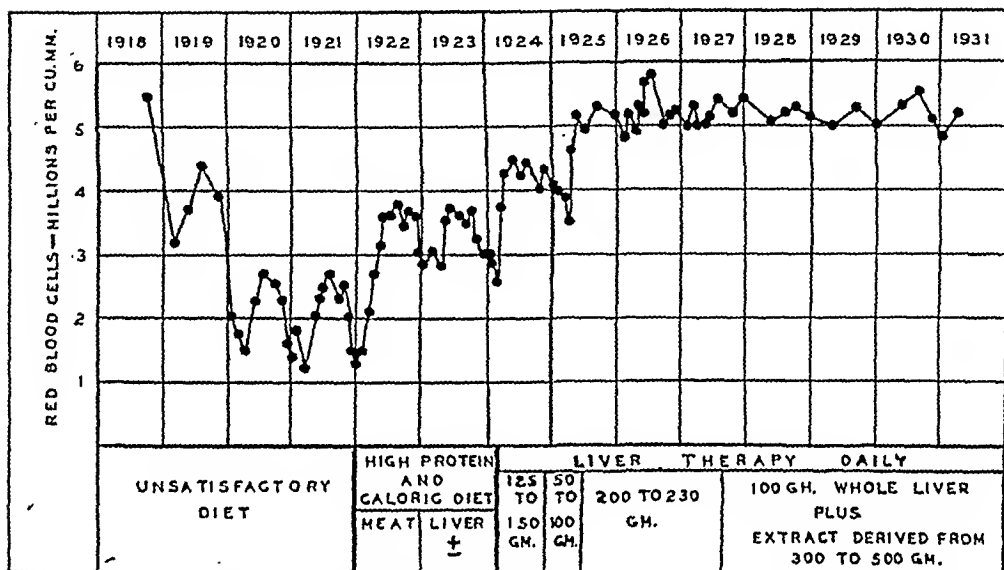


FIG. 2.—Red blood cell counts of a patient with pernicious anemia followed by Dr. George R. Minot over a period of 14 years.

During the years 1918 to 1921, while taking an unsatisfactory diet the red blood cell counts showed a progressive descent, with the lowest counts in the winter and the highest in the summer. During 1922 the patient was placed on a high caloric diet containing much animal protein (extrinsic factor) and the red blood cell counts averaged 1 million higher than during the 2 preceding years. In 1923 the patient began to take a little liver and later when placed on increasing amounts attained a normal red blood cells count which has been maintained for 7 years.

The tendency of the condition of patients with pernicious anemia to show "spontaneous" fluctuations has been frequently remarked in the past. The oscillating and progressive descent of the red blood cell count of a patient observed over a period of years by Dr. George R. Minot is clearly illustrated in Fig. 2,\* as well as the subsequent effect of continued liver feeding in permanently maintaining the blood count of the patient at a normal level. The annual depression of the level of the blood counts of this patient before treatment is strikingly seasonal, as in the relapses during treatment reported by Isaacs.<sup>40</sup> The number of untreated or relapsed cases of

\* Permission to present these data was kindly given the authors by Dr. George R. Minot.

this disease admitted to the Boston City Hospital during the winter months is somewhat greater than during the summer months. Seasonal fluctuations in the incidence of deficiency diseases, such as epidemic hemeralopia,<sup>41</sup> pellagra<sup>42</sup> and scurvy,<sup>43</sup> may be attributable to variations in diet factors. On the basis of our explanation of the immediate causes leading to the development of pernicious anemia, it is evident that fluctuations either in the amount of the extrinsic factor, in the diet or of the amount of intrinsic factor secreted by the stomach could cause variations in the amount of hematopoietic substance formed as a result of the interaction of these two factors. Moreover, we have presented evidence that after the administration of hematopoietic substance in the form of liver extract added to the diet, the intrinsic factor, known to be absent before this therapy, reappeared in the gastric juice of Case 41. Under these circumstances the essential function of the stomach of this patient was improved after the administration of the hematopoietic factor, perhaps thus representing a chemical improvement *of the function of the gastrointestinal tract just as the reappearance of the papillæ on the tongue of certain patients after treatment with hematopoietic substance represents a morphologic repair.*<sup>44</sup> This seems to us an observation of potentially great significance in its bearing on the explanation of the "spontaneous" fluctuations characteristic of the disease before its voluntary control was possible.

On this basis it is evident that if a patient in the early stages of pernicious anemia still had a certain amount of intrinsic factor in the gastric secretion an increase of the extrinsic factor in the diet would not only immediately increase the amount of the hematopoietic substance formed, but that the increase of the latter so brought about might shortly increase the secretion of the intrinsic factor. This, in turn, would lead to a still further increase of the formation of the hematopoietic product. On the contrary, if the extrinsic factor were diminished a decreased formation of the hematopoietic product would result and possibly later of the intrinsic factor. Due to this interaction of factors an unstable equilibrium peculiar to the conditions of the disease would obviously be created, with a tendency to proceed in one direction or the other beyond effects referable directly to variation in the amounts of extrinsic factor. Since in the fully developed disease less hematopoietic substance is necessary to maintain a low red blood cell level than a high one,<sup>14,45</sup> these marked fluctuations would not necessarily be either immediately disastrous or entirely curative. Even a reduced amount of hematopoietic product might for a time be sufficient to maintain a red blood cell count at a low level. On the other hand, since a normal red blood cell count could not be so easily maintained as one at a somewhat lower level, the patient would not necessarily regain an entirely normal blood even with a marked relative increase in the formation of the hematopoietic substance. Finally, with

the complete disappearance of the intrinsic factor, which we have found to be the case in all the patients with the fully developed disease, blood production would fall to a level incompatible with life.

This general explanation of the natural course of the disease is further suggested by the fact that before treatment with liver was used the most successful management of the patients seemed to be attained by the use of diets rich in animal protein,<sup>46,47</sup> and so probably containing much of the extrinsic factor. The effect of such a régime is shown by the distinct improvement of the blood level of a case of pernicious anemia after the institution of this treatment. (Fig. 2.) Since with the beginning of a remission the patient's appetite improves and the tendency is to eat more, the intake of of extrinsic factor would rise still further, while the ability of the body to utilize it in the formation of the hematopoietic substance might also improve. The evidence by analogy with the seasonal incidence of other deficiency diseases suggests that the "spontaneous" remissions and relapses were really due to slight fluctuations in the amount of the extrinsic factor in the food, thereafter effective in a magnified way in producing fluctuations in the red blood cell counts by the mechanism we have outlined. Of course, other general systemic conditions such as infections might affect the amount of secretion of the intrinsic factor<sup>48</sup> or even operate directly upon the bone marrow.<sup>49</sup> In contrast to the earlier natural history of the disease observed by others, we have seen in the course of observations on over 100 patients with pernicious anemia, under conditions in the hospital such that their intake of the extrinsic factor was controlled and probably small, only one striking "spontaneous" remission. It is possible that the periods of controlled observation of from only 10 to 40 days which we have used were not sufficiently long to provide opportunity for improvement such as occurred during the prolonged periods of rest and bed care formerly given these patients. It is, however, readily comprehensible that before the liver treatment of pernicious anemia remissions were common and inexplicable, since the mechanism which we believe to have an important bearing on this phenomenon was not then known, and so the essential factor not controlled.

#### APPENDIX OF CASE HISTORIES.

CASE 39.—R. W., aged 55 years, white, married, an American minister. Diagnosis: Sprue; chronic diarrhea; pernicious anemia. Admitted, March 24, 1930. Discharged, May 5, 1930.

*Pertinent History.* Ever since the patient was engaged in missionary work in China, 28 years ago, he had had spells of diarrhea, anemia and weakness. The stools at first, and sometimes after, were grayish, foamy, often contained mucus and sometimes blood. At the time of onset he also had malaria with recurrence of chills every fall. Seven years ago he was told that he had sprue and was given a diet containing some liver. Temporary improvement followed, but later he began to lose weight again and developed a sore tongue and sores within his nose. Four years ago he returned to the United States and was placed on a diet containing  $\frac{1}{4}$  pound of liver and 3 yeastcakes daily. On this régime he gained strength, until 4 months before entry, when he began to grow weaker, paler and to have more diarrhea, some palpitation on exertion and swelling of the ankles. He had had no paresthesias.



**Admission Examination.** The patient was a tall, somewhat emaciated, pale, white-haired man. The sclerae were clear and not jaundiced. The tongue was quite atrophic around the edges. The upper teeth were replaced by a plate and there were many false lower teeth. The lungs were negative. The heart showed a systolic murmur. The blood pressure was 125 systolic and 55 diastolic. The vessels were normal. The abdomen was negative. The deep reflexes were normal. The vibration sense was slightly diminished over the tibiae.

**Laboratory Reports.** *Urine:* Negative. *Stools:* Soft, light brown, no foam. Odor not offensive. Occult blood test, negative. No ova or amebae on inspection or culture. *Blood:* R. b. c., 1,510,000; w. b. c., 2650; hemoglobin, 39 per cent (Sahli); color index, 1.28. Differential: Polymorphonuclears, 40; lymphocytes, 48; mononuclears, 8; eosinophils, 4; basophils, 0 per cent. The red cells showed marked variation in size and shape, there being both microcytes and macrocytes and occasional basophilic cells. Nucleated red cells were rare. Platelets were normal in number, but occasionally a very large platelet was seen. *Gastric analysis:* Fasting contents, 60 cc. of slightly yellowish material containing no food; free HCl, 10; total acidity, 30. After 100 cc. of 7 per cent alcohol, at 20 minutes: free HCl, 27; total acidity, 59; at 40 minutes: free HCl, 53.5; total acidity, 60. After 0.5 mg. of histamin subcutaneously, at 20 minutes: free HCl, 70; total acidity, 76 cc. of  $\frac{1}{10}$  N HCl. These findings were essentially the same for samples of gastric juice on 8 successive days after the subcutaneous injection of histamin.

**Course.** During the patient's stay in the hospital clinical improvement took place after the first administration of liver and was followed by a gradual diminution of the number of loose stools and an increase of strength. On the day of discharge the blood count had reached only 2,015,000, with a hemoglobin of 56 per cent (Sahli), despite almost a month of therapy with potent extract derived from 800 to 900 gm. of liver daily.

**CASE 41.**—W. J., aged 41 years, white, male, an American salesman. Diagnosis: Dermoid cyst; chronic diarrhea; intestinal anastomoses; pernicious anemia. Admitted, March 30, 1930. Discharged, May 29, 1930.

**Pertinent History.** Nine years ago the patient was operated upon for a supposed retroperitoneal malignant condition at another clinic. He then received repeated Roentgen ray therapy, and several months later developed a fecal fistula into the sigmoid, from which, later, the discharge of a quantity of putty-like material together with hair led to a diagnosis of dermoid cyst as the original tumor. He then developed a second fistula into the small bowel, and during the next 4 years underwent 12 operations, by which numerous anastomoses and resections of the large bowel were performed. For the past 5 years he had suffered from varying degrees of ill health, exhibiting secondary anemia, marked loss of weight and a persistent watery diarrhea, requiring opium to keep the number of bowel movements as few as four or five daily. Beginning 2 years ago, and at intervals since, he had a sore tongue and transient paresthesia of the hands and feet. One year ago a blood examination showed: R. b. c., 2,000,000; hemoglobin, 60 per cent (Talqvist); color index, 1.5. Six months ago he was sicker and more anemic, but a diagnosis of pernicious anemia was rejected because the gastric analysis showed much free hydrochloric acid. However, at this time, on his own responsibility, he took liver extract for 2 weeks; he at once improved subjectively, and a few weeks later showed a higher blood count. He then discontinued liver extract, and in the 5 months before entry his symptoms increased and he took to his bed with persistent diarrhea, sore tongue and slight jaundice.

**Admission Examination.** The patient was pale, emaciated and had a slight jaundice of the sclerae and skin. The tongue appeared normal. The heart and lungs were essentially negative. The blood pressure was 85 systolic and 45 diastolic. The abdominal wall was very thin, showing peristalsis. There were many scars over the abdomen and a small fecal fistula in the left upper quadrant. The liver, spleen and kidneys were not felt. There was bilateral hydrocele. Slight pitting edema of both feet was observed. The reflexes and sensation were normal.

**Laboratory Report.** *Urine:* Clear, yellow, acid; specific gravity, 1.016; albumin, slightest possible trace; sugar, none; sediment, negative. *Stools:* Fermentative and watery; very acid; no gross blood; considerable mucus; occult blood test, moderately positive. *Blood:* R. b. c., 910,000; hemoglobin, 35 per cent (Sahli); color index, 1.9. W. b. c., 5350. The red cells were well filled with hemoglobin, showed much variation in size and shape and definite oval macrocytes. No abnormal white cells were seen. The platelets were somewhat diminished. *Gastric analysis:* Fasting contents not obtained. After 50 cc. of 7 per cent alcohol, at 20 minutes: free HCl, 0; total acidity, 6; at 40 minutes: free HCl, 0; total acidity, 7. After 0.5 mg. of histamin subcutaneously, at 20 minutes: free HCl, 52; total acidity, 71; at 40 minutes: free HCl, 83; total acidity, 89 cc. of  $\frac{1}{10}$  N HCl per 100 cc.

**Course.** The fasting gastric juice after histamin stimulation, which invariably contained much free hydrochloric acid, was recovered each day for several days and utilized in the observations carried out on Case 42. During this initial period of 10 days the patient received 200 gm. of beef muscle daily without evidence of clinical improvement. Immediately thereafter the patient was given daily Liver

Extract No. 343 (N. N. R.), derived from 300 gm. of liver. He showed prompt improvement clinically and by the reticulocyte response, as shown in Table 1. At the end of a month his blood showed: R. b. c., 1,940,000; hemoglobin, 48 per cent (Sahli); at the end of 2 months: r. b. c., 3,020,000; hemoglobin, 65 per cent (Sahli); at 3 months: r. b. c., 3,940,000; hemoglobin, 65 per cent (Sahli); at 4 months: r. b. c., 4,710,000; hemoglobin, 70 per cent (Sahli). The clinical improvement was commensurate: the diarrhea was less; the patient felt stronger, ate well and gained much weight.

CASE A.—C. D., aged 42 years, female, white, single, American. Diagnosis: Secondary anemia; hepatic enlargement. Admitted, February 3, 1930. Discharged, May 18, 1930.

*Pertinent History.* The patient was always well until about 5 years ago, when all her teeth were extracted because of mild rheumatic attacks. One year ago she began to lose weight and to become pale. At this time she noticed a tightness in the epigastrium coming on immediately after meals. After the teeth were extracted her diet became extremely limited. She ordinarily ate no breakfast; took crackers, toast and tea for lunch and for supper, and sometimes corned beef and cabbage at lunch or supper. She never observed any blood loss during this time.

*Admission Examination.* The patient was fairly well nourished. Her skin had a waxy pallor; the mucous membranes were very pale and without petechiæ. There was an iridectomy scar and external strabismus of the left eye. The vessels of the fundus were tortuous. All the teeth were replaced by a plate. The tongue showed a marked papillary atrophy. The lungs were clear. The heart was enlarged to left and right; the sounds were rapid, loud and forceful, with an increased aortic second sound and a systolic murmur over the precordium and axilla. The blood pressure was 110 systolic and 70 diastolic. The radial and brachial arteries were slightly thickened. The abdomen was slightly distended and a nontender mass with a smooth edge was felt at the level of the umbilicus in the right flank. The spleen was just palpable. There were large thrombosed bleeding hemorrhoids. There was some pitting edema of the ankles. The reflexes and sensation were normal.

*Laboratory Reports.* *Urine:* Cloudy, straw-colored, acid; specific gravity, 1.012; albumin, slight trace; sugar, none; sediment, 2 to 3 white blood cells per high-power field. *Stool:* Dark brown, formed; no gross blood or mucus. *Blood:* R. b. c., 1,280,000; hemoglobin, 9 per cent (Sahli); color index, 0.35. W. b. c., 3225. Differential: Polymorphonuclears, 80; lymphocytes, 10; mononuclears, 10 per cent. The red cells showed marked achromia and poikilocytosis. The platelets were somewhat reduced. The blood Wassermann was negative. *Gastric analysis:* Fasting contents: 5 cc. of clear, mucoid material; free HCl, 0; total acidity, 4. After 0.4 mg. of histamin subcutaneously, at 20 minutes: free HCl, 0; total acidity, 10 cc. of  $\frac{1}{10}$  N HCl per 100 cc. *Röntgen rays:* Bones showed no evidence of metastases. Kidneys apparently of normal size. Barium enema showed no gross abnormality. A large, soft tissue tumor, presumably liver, displaced the cecum and hepatic flexure toward the midline.

*Course.* The patient made striking improvement clinically on daily doses of iron ammonium citrate varying from 1 to 6 gm. At the end of a month on 1 gm. of iron ammonium citrate daily the blood examination showed: R. b. c., 2,795,000; hemoglobin, 36 per cent (Sahli); at the end of 2 succeeding months, on 6 gm.: r. b. c., 4,850,000; hemoglobin, 84 per cent (Sahli). During the early part of this therapy gastric juice was removed from the patient daily for 10 days and used in the observations made on Case 44.

CASE B.—H. R., aged 53 years, female, white, married, an Irish housewife. Diagnosis: Colitis; secondary anemia. Admitted, April 10, 1930. Discharged, July 14, 1930.

*Pertinent History.* The patient's health had usually been good except for a long-standing nonproductive cough. Four years ago she began to diet for obesity, reducing a fairly normal diet to tea, bread, occasionally lettuce and an egg or a little meat. One year ago she began to notice clots of blood in the stools. Four months ago she was much weaker and was told she looked pale. She became somewhat dyspneic on exertion and noticed a slight swelling of the ankles at night. The last menstrual period was a year ago. She lost 12 pounds in 4 years.

*Admission Examination.* The patient was a gray-haired, obese, rather sallow woman with distinctly pale skin and mucous membranes. There were faded purpuric spots on the right ankle. The tongue was almost completely devoid of papillæ. There was an upper plate and only a few lower teeth. The lungs were normal. The heart was somewhat enlarged to the left, with a soft systolic murmur at the apex. The blood pressure was 130 systolic and 80 diastolic. The abdomen was pendulous. There were small external hemorrhoids, not bleeding. There was a slight pitting edema of the ankles. There was no evidence of any neurologic disturbance.

*Laboratory Reports.* *Urine:* Faint trace of albumin; sediment; 5 to 9 w. b. c. per high-power field. *Stool:* Brown, unformed; no gross blood or mucus; negative for occult blood. *Nonprotein nitrogen:* 31.6 mg. per 100 cc. *Blood:* R. b. c.,

3,050,000; hemoglobin, 38 per cent (Sahl); color index, 0.62. W. b. c., 4150. Differential: Polymorphonuclears, 67; lymphocytes, 21; mononuclears, 9; eosinophils, 2; basophils, 1 per cent. The red cells showed marked achromia, anisocytosis and poikilocytosis. There were no abnormal white cells. The platelets were normal. The Kahn test was negative. *Gastric analysis:* Fasting contents: 45 cc. of cloudy, yellow fluid; free HCl, 0; total acidity, 13. After 0.5 mg. of histamin injected subcutaneously, at 30 minutes: free HCl, 0; total acidity, 15 cc. of  $\frac{1}{10}$  N HCl. *Röntgen rays:* Gastrointestinal tract showed a normal esophagus, stomach and duodenal cap, but evidence of external pressure from the gall bladder and delay in the second position of the duodenum. Marked hyperperistalsis was noted throughout the bowel. A barium enema showed complete absence of haustration in the transverse colon and general irritation. Proctoscopy showed a small ulcer within the rectum.

*Course.* Beginning 3 days after entry the gastric juice of this patient was collected daily for 10 days and used in the observations on Case 45. The patient was then given small doses of iron which showed no effect on blood formation within 10 days. Later, she was given iron in large dosage and gradually recovered from her anemia.

**CASE C.**—L. G., aged 53 years, male, white, a single Portuguese stationary engineer. Diagnosis: Subacute combined degeneration of the spinal cord; hypertrophic arthritis of the spine. Admitted, April 25, 1930. Discharged, November 17, 1930.

*Pertinent History.* Aside from minor traumatic injuries the patient was well until the present illness. He worked as a fireman until 9 years ago, since then as an engineer. His diet had always contained meat, fruit and vegetables; he had never used alcohol or drugs. His appetite had always been excellent; his bowels fairly regular. On rare occasions he had vomited a little after a hearty breakfast. A month ago, after an unusual exposure to moisture while at work, he noticed pain in the left elbow radiating to the left shoulder and chest, especially on motion. Two days later both legs became weak, and he had a feeling as of pins and needles in the soles of his feet. He had no chills or fever.

*Admission Examination.* The patient was well developed and nourished, with good color. The tongue was normal. Aside from very bad teeth and enlarged inguinal glands, all positive findings were related to the neurologic examination. The optic disks were slightly pale. The strength of the arms was normal. All muscle groups of the left leg were weaker than those of the right. The arm reflexes were hyperactive. All abdominal reflexes were absent. The ankle and knee reflexes were hyperactive, with a well-sustained ankle clonus on the left and a few jerks on the right. Bilateral positive Babinski reactions were obtained. Position sense of the toes was absent. The vibration sense was absent on the left tibia and much impaired on the right. The gait was slow and spastic. The patient was mentally normal, but poorly educated.

*Laboratory Reports.* *Urine:* Negative. *Blood:* R. b. c., 5,360,000; hemoglobin, 90 per cent (Sahl). W. b. c., 7300. Differential: Polymorphonuclears, 80; lymphocytes, 14; mononuclears, 3; eosinophils, 1; basophils, 2 per cent. The red cells were normal in size and shape and normally filled with hemoglobin. There were no abnormal white cells. The platelets were normal. The blood Wassermann was negative. *Gastric analysis:* Fasting contents: free HCl, 0; total acidity, 14 cc. of  $\frac{1}{10}$  N HCl per 100 cc. After 50 cc. of 10 per cent alcohol, at 15 minutes: free HCl, 0; total acidity, 3; at 30 minutes: free HCl, 0; total acidity, 9. After the subcutaneous injection of 0.8 mg. of histamin, at 15 minutes: free HCl, 0; total acidity, 11; at 30 minutes: free HCl, 0. *Lumbar puncture:* Normal dynamics and pressure. Spinal fluid, clear, colorless, cell-free. Globulin test, negative. Total protein, 37 mg. per 100 cc. Wassermann, negative. Colloidal-gold curve, 0000000000. *Röntgen ray:* Dorsal spine showed extensive hypertrophic arthritis. Cervical spine, negative.

*Course.* The gastric juice of this patient was removed daily after the subcutaneous injection of histamin and used in the observations made on Case 46. Subsequently the patient made considerable improvement under treatment with vitamin B and raw liver.

**CASE D.**—A. L., aged 28 years, female, white, a single American. Diagnosis: Chlorotic anemia of pregnancy. Admitted, September 29, 1930. Discharged, October 27, 1930.

*Pertinent History.* The patient was always healthy until she became pregnant, 9 months before admission. She had always been somewhat pale and had a sister who became anemic during pregnancy. During the gestation period the patient became increasingly pale. She became somewhat short of breath on exertion during the latter months and had some edema of the ankles just before delivery. She maintained a good appetite, and ate as usual a diet consisting mainly of starches with rarely vegetables and meat. She was somewhat constipated. She had no sore tongue, paresthesia, loss of blood or urinary symptoms. She was delivered of a normal male child 3 days before entry without unusual loss of blood.

*Admission Examination.* The patient was moderately well nourished; the skin and mucous membranes were very pale. There was evidence of much dental work. The tongue was extremely smooth and atrophic. The rest of the examination was

negative except for a soft blowing systolic murmur over the apex of the heart. The reflexes were normal.

*Laboratory Reports.* *Urine:* Negative. *Stools:* Negative. *Blood:* R. b. c., 3,325,000; hemoglobin, 36 per cent (Sahli); color index, 0.54. W. b. c., 11,450. *Differential:* Polymorphonuclears, 76; lymphocytes, 18; mononuclears, 4; eosinophils, 2 per cent. The red blood cells varied in size and shape and were markedly achromic. The platelets were increased. The blood Wassermann was negative. *Gastric analysis:* Fasting contents: 25 cc. of fluid: free HCl, 0; total acidity, 13. After 50 cc. of 7 per cent alcohol, at 20 minutes: free HCl, 0; total acidity, 7. After 0.8 mg. histamin, at 15 minutes: free HCl, 0; total acidity, 7; at 30 minutes: free HCl, 0; total acidity, 5 cc. of  $\frac{1}{8}$  N HCl per 100 cc.

*Course.* During a period of 10 days gastric juice was daily removed after histamin stimulation for use in the observations made on Case 47. The patient was then given iron ammonium citrate in 6-gm. daily doses, which resulted in a prompt reticulo-cyte response and increase of red blood cells followed by rapid clinical improvement.

**Summary and Conclusions.** 1. Certain apparent exceptions to the hypothesis that pernicious anemia is produced by an inadequate gastric digestion of protein, thus causing a virtual deficiency in the presence of a normal diet, have been examined and found to offer no exception to the theory.

2. The experiments given below confirm the negative evidence of those of the three preceding papers of this series, and demonstrate positively that the existing tests for hydrochloric acid, pepsin and rennin of the gastric juice are not necessarily related to the presence or absence of the intrinsic factor of normal human gastric juice essential to the reaction with beef muscle described in these papers since:

A. *The intrinsic factor was absent from the otherwise normal gastric contents of 2 cases of pernicious anemia in relapse.*

(1) To each of 2 patients with the blood picture of pernicious anemia, but with an apparently normal gastric contents, beef muscle was given daily for 10 days without effect on blood formation.

(2) The fasting gastric juice of each of these 2 patients, secreted after histamin injection, was incubated daily with beef muscle and the resulting material given respectively to 2 typical cases of Addisonian pernicious anemia without effect on blood formation in either case within 10 days.

(3) Each of the 2 patients whose gastric juice was thus found to have no specific effect on beef muscle subsequently reacted positively to comparable doses of liver or liver extract by mouth.

B. *The intrinsic factor was present in the otherwise achyllic gastric contents of a patient without anemia and of 3 patients with hypochromic anemia.*

(1) The gastric juice of a patient with no evidence of any disturbance of blood formation, and the gastric juice of each of 3 patients with hypochromic anemia were found even after histamin stimulation to contain no free hydrochloric acid and little or none of the common enzymes of the normal stomach.

(2) The fasting gastric juice of each of these 4 patients, secreted after histamin stimulation, was incubated daily with beef muscle and the resulting material administered respectively to 4 typical cases of Addisonian pernicious anemia with positive effects on blood formation in each case within 10 days.

3. In 1 of the cases of pernicious anemia with an apparently normal gastric juice, the intrinsic factor shown to have been absent in relapse was found to be present after the remission induced by liver extract.

4. The facts concerning the extrinsic and intrinsic factors and their relationship to their hematopoietic product described in this and our previous papers have been considered in relation to the age incidence of the disease and the tendency to spontaneous fluctuations of the blood count formerly noted.

5. Evidence for an accessory rôle in the etiology of pernicious anemia of a difficulty with the absorption of hematopoietic substance at least in certain cases of the disease is presented.

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## HODGKIN'S DISEASE OF BONE MARROW AND SPLEEN WITHOUT APPARENT INVOLVEMENT OF LYMPH NODES.\*

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IN Hodgkin's<sup>1</sup> original article, "Morbid Appearances of the Absorbent Glands and the Spleen," which was published in 1832, 7 cases were described which all showed splenic and lymphoid enlargement. Today, to be sure, they would not be all recognized as true Hodgkin's disease. There was naturally no mention made of the bone marrow by Hodgkin's paper, as this tissue was not an object even of gross study until after Neumann's studies some 40 years later. Ever since Hodgkin's time the lymph nodes and the spleen have been considered the chief organs to be involved in Hodgkin's disease as we know it today, though various atypical pathologic types have been emphasized depending on the greater prominence of one or other group of involved organs. Thus "splenic Hodgkin's disease" is spoken of when the primary or most marked lesion occurs in this organ. In abdominal Hodgkin's granuloma the mesenteric or retroperitoneal nodes show the most prominent lesions (in a few cases that we have seen massive involvement of these nodes was accompanied by little or no change else-

\* Read before the Philadelphia Pathological Society, May 14, 1931.

where); in the rarer gastrointestinal form the lesions may be almost entirely restricted to the mucosa and adjacent lymph nodes. Bone marrow lesions are not uncommonly found histologically (30 to 40 per cent, Ziegler;<sup>2</sup> 50 per cent, Symmers<sup>3</sup>), as one would expect in a disease chiefly involving the hemolytopoietic system. Cutaneous involvement is far from rare and the characteristic lesions also have been found in many other organs, such as the bones, "thyroid, pancreas, adrenal, heart and voluntary muscles, esophagus, breast, tonsils, ovary" (Ewing<sup>4</sup>). A typical case in the uterus has also been described. Dr. Strumia is reporting tonight such a case of unusually wide distribution. The commonest type, however, still remains that in which the several chains of superficial lymph nodes are involved, usually the cervical, axillary, inguinal, etc., though even here Ewing<sup>4</sup> and Symmers<sup>3</sup> consider that these may be the superficial manifestation of a primary internal involvement.

As far as I have been able to find, however, there has been no case reported in which the involvement was chiefly of the spleen and bone marrow, and where no lymph node involvement could be found. In Symmers',<sup>5</sup> Dowd's<sup>6</sup> and Wade's<sup>7</sup> cases of the splenic type no superficial lymph nodes were found involved, or abdominal nodes at operation, but these cases did not come to autopsy. As the present case has already been referred to by Rolleston,<sup>8</sup> in his Schorstein Lecture on Hodgkin's disease, and as it must be of considerable rarity, it seems desirable to put it on public record. It is, of course, impossible entirely to rule out all lymph node involvement in this case, though especially careful search was made at the time of autopsy. As Fraenkel<sup>9</sup> well notes, "It may happen that the majority of the lymph nodes seen macroscopically and microscopically have seemed to have been spared and that only in one spot may a small lymph node be involved. In a case of the author's this occurred in the supraclavicular fossa." It is obvious that in order completely to rule out lymph node involvement this would necessitate serial section of all lymph nodes of the body—an impossible task. Short of this we can only state that a very careful examination failed to reveal any involvement of lymph nodes and that the bone marrow and splenic lesions were undoubtedly of prime importance and that one or the other was in all probability the primary site. The absence in this case of lymph node material for histologic study is regrettable, but, on theoretical grounds at least, there is the consolation that even completely negative results in several nodes would not meet the objection above referred to. An excellent review of the whole subject of Hodgkin's disease has recently been published by Simonds.<sup>10</sup>

**Case Report.** M. D. (1925—242), a white male, aged 55 years, was admitted to the medical ward (service of Dr. Boston) of the Philadelphia General Hospital on November 25, 1924, complaining of weakness in the legs.

The patient, a painter by occupation, lately has noticed weakness in his



legs upon ascending stairs. He has been short of breath for about 6 months; at present when he attempts to go upstairs he gets short of breath, dizzy, and his heart begins to beat very fast. He has profuse nocturia, passing large quantities of urine, from 2 to 3 quarts a night. His appetite has been poor and bowels constipated, with periods of diarrhea. He lost 15 pounds in the last month and has had numbness, weakness and cramps in his legs and arms.

*Past History.* He had scarlet fever when a child, and has had pneumonia.

*Social History.* A painter all his life, he has never had colic. He had gonorrhea in boyhood; denies chancre; has been a moderate drinker of alcohol. His family history is negative; no familial tendencies.

*Physical Examination.* The patient is an elderly white adult male, lying comfortably in bed. The skin is generally a pallid, yellow color; there is no edema, cyanosis or dyspnea. The eyes, ears and nose are negative. There is facial weakness on the left side, and the tongue deviates to the left with a coarse tremor. The teeth are carious. Neck: Venous pulsations are seen on both sides; there are no palpable lymph nodes. Chest: The breath sounds are easily heard and apparently normal. The heart is negative. The pulse is accelerated but regular; it is small in volume. The blood pressure is 120 systolic and 50 diastolic. The abdomen is prominent in the upper half, with muscle spasm over these parts. The lower edge of the liver reaches the level of the umbilicus. The spleen extends to the level of the anterior superior spine. The extremities are negative.

*Laboratory Tests.* *Urine:* Heavy trace of albumin. Specific gravity, 1010. Hyalin and granular casts, red and white blood cells, few in number. Negative for urobilin. *Blood:* The Wassermann test is negative with both antigens. Blood chemistry: nonprotein nitrogen, 60 mg.; uric acid, 7 mg.; creatinin, 2 mg.; sugar, 150 mg. Hemolysis: begins at 0.46 per cent NaCl; is complete at 0.32. The platelets number 186,000 per c.mm. The blood serum is negative for the vanden Bergh reaction. On admission the erythrocytes numbered 1,070,000 per c.mm., with anisocytosis, poikilocytosis and polychromatophilia; leukocytes, 8200 (78 per cent polymorphonuclears, 19 per cent lymphocytes). February 5, 1925: Erythrocytes, 1,116,000; leukocytes, 3700 (54 per cent polymorphonuclears, 43 per cent lymphocytes). Hemoglobin, 4.4 gm. No stippling. *Feces:* Urobilin, 1600 units (Addis).

*Progress.* The patient was transfused several times but gradually weakened and died on March 24, 1925.

*AUTOPSY ABSTRACT.* Autopsy (9679, 1925—242) was performed by Dr. Palomeque 6 hours after death. The body weighs 125 pounds and is 170 cm. long, well developed and well nourished. There is marked pallor of the skin and mucous membranes. The gums are devoid of teeth. The neck is somewhat muscular and shows no palpable glands on careful examination. The thyroid is normal, the chest wall barrel shaped. The abdomen, large and protuberant, with definite fullness along the left external aspect and in the right superior quadrant. The lower half is distended. The thighs show normal muscular development but are very flabby, with moderate edema of the ankles. There are no lymph node enlargements in the axilla, groin, popliteal or other spaces.

*Internal Organs.* A substantial layer of fat of the abdominal wall measures 4 cm. in depth. There are about 3500 cc. of light, straw-colored fluid in the peritoneal cavity. No abnormal lymph nodes are found in the mediastinum, mesentery or retroperitoneum. There are about 1000 cc. of pale clear straw-colored fluid in the left pleural cavity and 1200 in the right. The pericardium is markedly distended and contains about 500 cc. of slightly turbid fluid.

*Spleen.* The spleen occupies the whole left side of the abdomen, extending to the anterior axillary line and down to the anterior superior spine of



FIG. 1.—Histology of the femoral marrow, showing Hodgkin involvement, fibrosis and persisting hemolytopenia. ( $\times 100$ .)

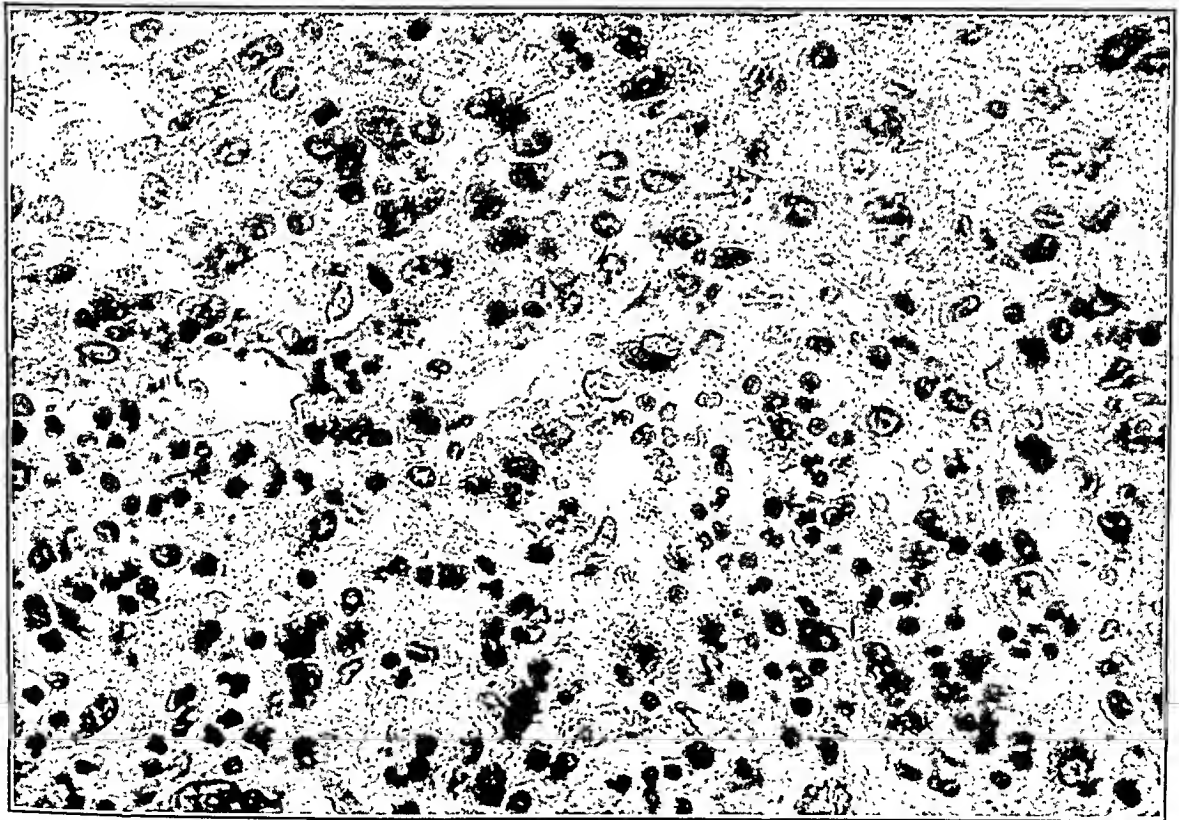


FIG. 2.—Histology of the tibial marrow, showing an earlier stage (*i. e.*, less fibrosis) of the same picture—endothelioid, Dorothy Reed cells, lymphocytes, polymorphonuclears, etc. The eosinophilic myelocytes can be made out on close inspection. ( $\times 560$ .)

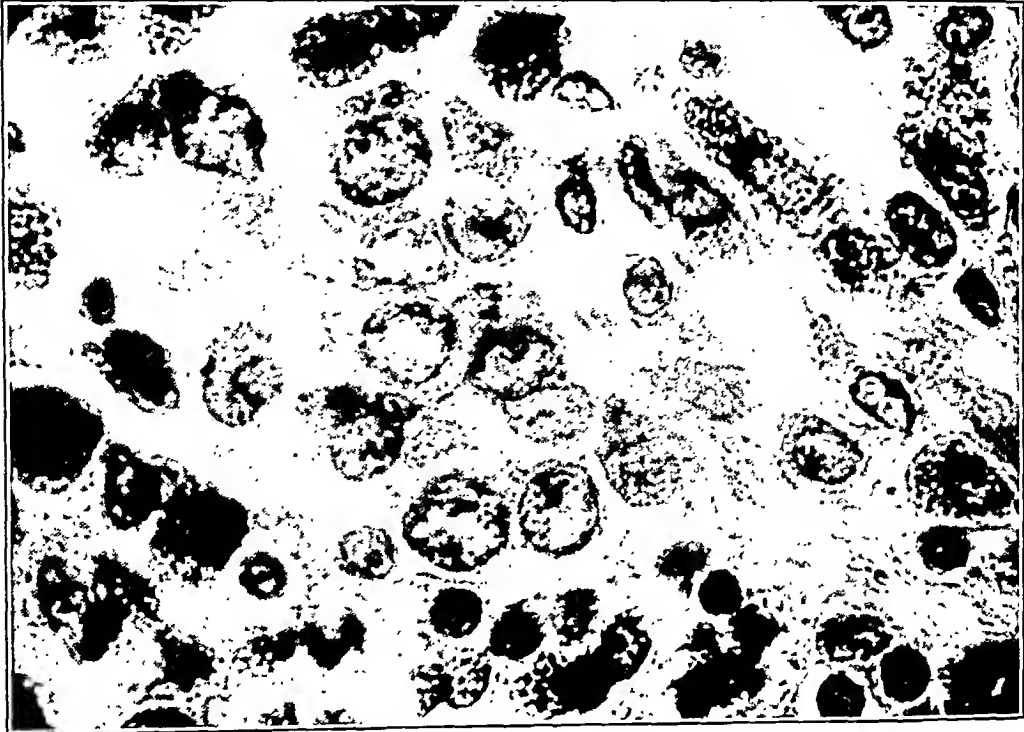


FIG. 3.—The same high power. The coarse granules of a dozen or more eosinophilic myelocytes can easily be distinguished. ( $\times 1400$ .)

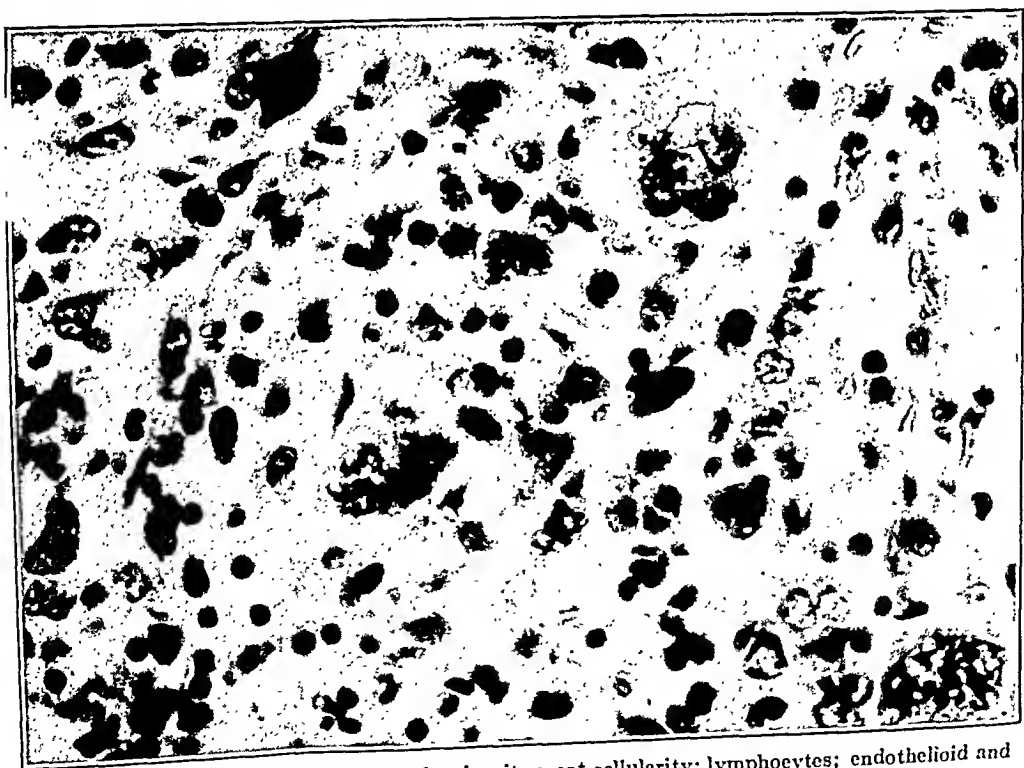


FIG. 4.—Histology of the splenic pulp, showing its great cellularity; lymphocytes; endothelioid and Dorothy Reed cells and eosinophilic myelocytes are numerous. ( $\times 840$ .)

the ileum. It weighs 1090 gm. and measures 22 by 16 by 7 cm. It is of triangular shape, showing distinct lobulations. The capsule is grayish-white and tensely stretched on the splenic tissue and without thickenings or adhesions. The organ cuts with increased resistance, showing a homogeneous pinkish-red color, smooth and glistening and very firm. The lymphatic follicles are not visible. A few trabeculae can be made out. There is no congestion and no blood is scraped from its surface. The splenic artery is sclerosed, of normal caliber, patent throughout. The splenic vein is somewhat larger than the artery and slightly sclerosed.

*Heart.* The heart is large, weighing 500 gm. There is definite hypertrophy of the right side with moderate fatty infiltration. On the left side there is moderate fibrosis of the musculature. The valves are of apparently normal size and show no marked lesions. The coronary vessels show only slight sclerosis, as does the aorta.

*Lungs.* The lungs show nothing noteworthy beyond slight emphysema.

*Adrenals.* The adrenals are apparently normal.

*Kidneys.* The kidneys weigh 200 and 220 gm. respectively, and are reddish-brown and firm. The capsule strips with slight difficulty, showing a granular surface which cuts with difficulty. The striations are obscured. The pyramids are pale and firm. The bloodvessels show moderate sclerosis. There is one large urinary retention cyst, 15 mm. in diameter, on the left kidney. Chronic arteriolar nephrosclerosis.

*Liver.* The liver weighs 2190 gm., appears very large, brown in color and fairly firm with rounded edges. It cuts with increased resistance, the cut surface being smooth and glistening, and shows numerous small whitish areas. There is an increase of fibrous tissue and a moderate congestion. Moderate cirrhosis.

*Gall Bladder and Pancreas.* Normal. The pancreatic artery is sclerotic.

*Vena Cava and Portal Veins.* Negative.

*Digestive Tract.* The *esophagus* is normal.

*Stomach.* Normal with smooth and glistening mucous membrane. No lesions found.

*Duodenum, Jejunum, Ileum and Colon.* Apparently negative, except for some congestion.

*Genito-urinary Tract.* No gross lesions.

*Prostate.* Small and atrophic.

*Seminal Vesicles.* Apparently normal.

*Bone Marrow.* The middle third of the right femur shows the marrow pinkish-red in color and hyperplastic. The marrow of the upper third of the right tibia shows a distinct hyperplasia, the medullary canal, containing flabby, pinkish-red marrow with a decreased amount of fat.

*Brain.* Is very pale and shows slight atrophy of convex surface and slight arteriosclerosis.

*Histologic Examination.* Examination of heart, lung, kidneys, esophagus, stomach, duodenum, pancreas and adrenal confirm the picture given in the gross inspection. In none of the lymphoid collections of the mucosae were any abnormalities found. The lung shows in addition to the emphysema some carbon and "heart failure" cells but nothing resembling Hodgkin's infiltrations.

The *liver* (of which an extremely small piece was taken for section) does not include any of the whitish nodules mentioned. It shows slight thickening of the capsule, general slight diffuse increase of loose fibrous tissue, congestion and atrophy of the liver cords, with deposition within the liver cells of granules of brownish pigment. In some areas the liver cells have an indefinite outline and take a paler acid stain, as if degenerated. A few large mononuclear and multinuclear cells are found in the sinuses, that are of the Hodgkin type.

*Spleen.* The capsule is thickened and shows spots of adhesions. The pulp shows a scarcity of Malpighian follicles, which are small and without so-called "germinal centers." Immediately beneath the capsule (to the depth of 1 low power field) it is definitely poorer in cells than deeper in. In the deeper areas it presents a fairly homogeneous appearance, due to a variety of cells scattered through a matrix of slightly but definitely increased delicate fibrous tissue. The small sinuses can thus be more easily identified, and are closely lined with cuboidal (not flattened) endothelial cells. In the pulp the most striking cells are eosinophilic myelocytes scattered diffusely, but in some areas composing more than half of the cells found. They are even found in small numbers in the follicles. Next most prominent (and probably more numerous) are the pleomorphic large Hodgkin cells, varying much in size, with pale to dark staining nuclei, and with chromatin both clumped and finely divided in different cells. The long thin varieties have the paler nuclei and their appearance merges with that of fibroblasts. The round, dark-staining varieties occasionally are multinucleated (Dorothy Reed cells); their nuclei vary from a vesicular type, with a few chromatin dots, to solid opaque chromatic masses (pyknotic, in the sense of condensation, but without reduction in amount of chromatin). Lymphocytes occur in moderate numbers; polymorphonuclears and hemosiderin are both rare. No other hemopoietic cells are recognized. In the subcapsular zone, the cells are much rarer, disclosing the fibrous framework and sinus outlines more clearly, also some erythrocytes in both sinuses and polyp. Blood-vessels and trabeculae present little of note.

*Bone Marrow.* Femur: To the naked eye the section has the appearance of a solid tissue, such as lymph node. Under low magnification the marrow is seen to be entirely made up of hemolytotoxic cells and fibrous tissue. If it were not for an occasional bone spicule, it could not possibly be recognized as bone marrow. In the more cellular areas interspersed through a rather loose fibrous tissue are various cells, of which the most prominent are megakaryocytes, and the eosinophilic myelocytes and mononuclear and multinuclear "endothelioid" cells, like those described in the spleen. Neutrophilic myelocytes and various immature cells of the erythrocytic series occur in moderate numbers. One perivascular collection of lymphocytes suggests a lymphopoietic focus.

This appears to be a combination of an extensive but late (fibrous stage) Hodgkin involvement of the marrow with persisting hemopoiesis.

In the tibial marrow the cellularity is much greater and the fibrosing process much less advanced than in the femoral marrow. Except that erythrocytes and pigment bearing phagocytes are somewhat more common, no essential differences in the quality of the cells concerned can be found from those of the femoral marrow. The immature erythrocytic cells are somewhat less frequent and pyknotic nuclei more so.

**Summary.** 1. A fatal case of Hodgkin's disease with autopsy is reported that was practically limited to the spleen and bone marrow, though in these two organs the involvement was extensive. The histologic appearance of the femoral suggests that the disease process may have been primary in this tissue. Absolutely no lymph node involvement could be found and the lymphoid tissue of the gastro-intestinal tract was histologically unchanged.

2. While this does not constitute unequivocal proof of the absence of lymph node involvement, it points strongly in that direction; while the absence of lesions in the mucosae and of the so-called germinal centers in the spleen suggest interesting speculations as

to the type of cell (reticular or endothelial) in which the disease process originates. It is suggested that the disease should be considered a disease of the hemolytopoietic or reticuloendothelial systems rather than of lymphoid tissue.

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## CARDIAC PAIN AND SUDDEN DEATH,\*

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IN the lay mind, at least, cardiac pain is inseparably connected with sudden death; in fact, any form of heart disease is regarded as possessing that probability. It is only within recent years that the luxury of a sudden death has begun to be appreciated, and for centuries men have prayed to be delivered from this desirable ending.

There are two widespread fallacies regarding sudden unexpected death that are difficult to eradicate from the popular belief. The first, common to both laity and medical profession, is that most cases of sudden death are due to some form of apoplexy. Apoplexy does occur suddenly, but rare indeed is the death therefrom sudden. Rare cases of a pontine hemorrhage breaking into the fourth ventricle do occur, in which death is practically instantaneous, and rare also are those cases of rupture of small aneurysms on the circle of Willis which may cause actually sudden unexpected death. But the erroneous belief is widespread in the medical profession, and in the lay mind alike, that apoplexy is a frequent cause of sudden death.

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VOL. 182, NO. 6.—DECEMBER, 1931      27

The second fallacy, especially in the lay mind, is that any form of heart disease means the probability of sudden death. While it is true that the majority of instances of sudden unexpected death do occur in some forms of heart disease, yet statistics show unmistakably that the number of sudden deaths compared with the total number of deaths from cardiac diseases is really small.

In New York City, in 1924, 22 per cent of the total deaths were due to some form of heart disease, but only 4 per cent of these were recorded as due to acute endocarditis, acute myocarditis and angina pectoris, and only 2.5 per cent were due to angina alone. Ninety-one per cent of the deaths from acute endocarditis and myocarditis and 85 per cent from angina pectoris were reported through the Medical Examiner's office, indicating probably a sudden and unexpected death, or at least one unattended by medical care.

As is well known, however, in the chronic valvular diseases of the heart, and in the usual forms of chronic myocardial diseases, death comes in the vast majority of patients with the slow cardiac failure, and although death may be sudden, it is not unexpected.

During such infectious diseases as typhoid fever, yellow fever, smallpox and diphtheria, the acute intense myocardial degeneration may at times be the cause of sudden death.

Warthin has reported 8 cases of acute syphilitic myocarditis which were acute exacerbations of chronic syphilitic myocardial degeneration, in all of which the death was sudden, and in 3 of which it was both sudden and unexpected.

A frequent cause of sudden, unexpected death is a chronic fatty degeneration of the myocardium. Brouardel emphasizes the fact that these patients often look well, that they have but slight dyspnea and never any attacks with severe symptoms, or pains of anginal type, their physical examination reveals nothing and that they do not always have an undue amount of body fat. Brouardel has seen this condition in poorly nourished children; it also occurs in those who take excessive amounts of alcohol, with but little exercise.

In the myocardium there is infiltration of fat between the muscle fibers and a fatty degeneration of the myocardial fibers themselves, the yellow, brown, red faded leaf color of the soft heart wall is characteristic.

The cause of this suddenness of death in these patients is not clear. A possible suggestion may be ventured that, as in diphtheria, the atrioventricular bundle may be degenerated separately, or in conjunction with the contracting mass of the myocardium. Mönckeberg reports 21 cases of diphtheria in which the atrioventricular bundle was the seat of excessive fatty degeneration, in 5 of which the degeneration of the tissue was excessive. In only 1 of these cases did the myocardium show destruction equal to that of the atrioventricular bundle, and in only 6 instances did it show a fatty degeneration. In several instances the myocardium showed fibroid



degeneration, while the bundle showed severe fatty degeneration. The conducting system, therefore, of the heart in consequence of its partially independent blood supply can also be independently diseased. How frequently the lesions of the conducting system, independent of either the contracting myocardium, or the coronary system, produce sudden death, is as yet unknown.

Brouardel quotes Forbes as reporting that of 64 cases of angina, 49 (76.5 per cent) died suddenly. In those patients who survive one attack of angina, whether this symptom complex arises from coronary thrombosis, or is of aortic origin, with no occlusion of the coronary vessels, sudden death is not unexpected. Sudden and unexpected death in the first attack of aortic or noncoronary angina is not the usual occurrence. Wenckebach even reports that he has never seen such a death, but it is not a great rarity.

Both Kolisko and Brouardel record that sudden unexpected death occurs not infrequently from embolisms of the vessels of the heart, or thrombosis of the pulmonary artery, the emboli coming chiefly from varicose veins of the legs, or occurring postpartum or postabortum. Sudden death from such emboli may occur following abdominal or pelvic operations, and probably it is of sufficiently common occurrence to have occurred in the experience of most surgeons. Usually the patient has a warning feeling of sickness, dyspnea or cyanosis coming on suddenly, followed quickly by loss of consciousness and death. At times death is so sudden and unexpected that the patient seems to crumple up dead; at other times the clot lodges in a coronary artery, with death in a few hours, or after a longer period of time, as from primary thrombosis of the coronary arteries.

The statistics of Krumbhaar and Crowell present 654 cases of spontaneous rupture of the heart; 58.3 per cent occurred in males and 41.7 per cent in females; in 80 per cent of these cases it occurred in the left ventricle, in 10 per cent in the right ventricle, in 5 per cent in the right auricle and in only 2 per cent in the left auricle and in the interventricular septum with rupture of both ventricles simultaneously, or the exact site not definitely stated in 2 per cent. The long descending branch of the left coronary is most frequently thrombosed, usually producing an infarct near the apex and involving the septum. This occurred in 60 per cent of the cases, and in 23 per cent of the cases it was in the transverse branch of the left coronary supplying the posterior wall of the left ventricle, in which the thrombosis occurred. Spontaneous rupture of the heart is due in the great majority of cases to antecedent coronary disease, often with actual thrombosis and acute infarct, or subsequent degeneration of the muscle fibers with stretching of the thinned wall and final rupture with or without terminal necrosis of the fibers. These cardiac ruptures rarely occur before the age of 45 years, more often between the ages of 50 and 60 years, and in the greatest number of instances between the ages of 60 and 80 years.



It is interesting to note that in less than 25 per cent of 325 patients dying from rupture of the heart reported by Nuzum and Hagen was there any clinical suggestion of heart disease previous to the cardiac rupture. In the 75 per cent who gave no history of heart disease previous to the rupture the majority did not suffer both sudden and unexpected death. Where the death was not sudden, it did not occur for a few hours to two days after the beginning of the symptoms. Of 400 of the cases reported by Krumbhaar and Crowell, however, in 72 per cent the death was "sudden."

Thrombosis of the coronary artery without rupture of the heart is probably the most common cause of sudden and unexpected death.

Experimental ligation of the coronary arteries as well as blocking with lycopodium spores indicates that sudden death occurs when a sufficiently large area of myocardial tissue is deprived of its blood supply, death being caused by ventricular fibrillation.

The abundant anastomoses between the branches of the same coronary and between the right and left coronaries may at times protect the myocardium, even when large branches are suddenly occluded. When, however, the occlusion occurs at the origin of the coronary artery, due to atheromatous involvement at its origin in the aorta, sudden death may occur.

In bacterial endocarditis emboli at times go into the coronary arteries and cause sudden death; if the disease has been recognized death may be sudden, but not unexpected.

Excessive exertion or intense emotion may cause death suddenly, and often unexpectedly, in any excessive myocardial degeneration. Sexual intercourse produces one of the severest strains which a degenerated heart can suffer; sudden and unexpected death during coitus is a very common occurrence in aged men.

Tumors in the brain may be present and unsuspected, and specially gliomata may cause sudden and unexpected death through hemorrhage from rupture of their bloodvessels. Pachymeningitis hæmorrhagica may cause death, but it is a slow death like that from apoplexy.

In children tuberculous and other forms of meningitis may cause sudden and unexpected death before the disease has clearly manifested itself, and may be unrecognized. In diphtheria the sudden death is too familiar to be unexpected, and it may be caused either by laryngeal suffocation from edema of the glottis, or cardiac paralysis, for in cardiac paralysis the atrioventricular bundle is often diseased as well as the main contracting system of the myocardium.

The most unexpected and sudden death in apparently healthy children is a so-called thymic death. The child may turn white and die instantly, or be found dead when supposed to be taking a nap. The actual cause of this form of sudden death is unknown. One opinion is that death is caused by pressure on the heart and

trachea as the enlarged gland lies on the pulmonary artery and aorta, and covers the right auricle and two-thirds of the right ventricle. In the narrow opening of the thorax the pressure of the trachea and the larynx may cause spasm of the glottis, or pressure on the recurrent nerves may cause paralysis of the larynx. Timme's explanation of the cause of this form of death is that to overcome the effect of the characteristically small vessels, low blood sugar and consequent asthenia increased demands are put upon the adrenals. The thymus, pressing on the vagus and sympathetic plexuses about the base of the heart and great vessels, causes the maladjustment of the automatic regulatory control which enables the body to meet emergencies. Slight excess pressure on the vagus may stop the heart, and the adrenal system, which is pushed too much, cannot meet the emergency, and the heart stops beating and the patient dies.

Status lymphaticus produces a condition in which sudden unexpected death not infrequently occurs; this condition occurs most frequently between 20 and 40 years of age. In 5652 necropsies in Bellevue Hospital in New York, Symmers found 457 cases of this condition; of the 249 cases analyzed 118 were active, 89 were recessive and 42 were partial. The sudden unexpected deaths occurring at the onset of some infectious diseases as cerebrospinal meningitis and at the beginning of general anesthesia have been attributed to this condition. In status lymphaticus the rupture of the hypoplastic arteries, usually one of the basal arteries of the brain, has been in rare instances the cause of sudden and unexpected death.

Hemorrhages from the lungs of such volume as to cause sudden death are not uncommon; in New York City about 2 a month are reported to the Medical Examiner's office. These hemorrhages usually come from the walls of a tuberculous cavity.

Hemorrhages from the esophagus may also cause sudden death. These hemorrhages may be due to a cancerous growth of the esophagus eroding into the aorta, or to an aneurysm of the aorta eroding into esophagus.

Rarely, but more often than is usually clinically realized, in cirrhosis of the liver sudden fatal hemorrhage may occur from a rupture of the ring of varicose veins at the junction of the esophagus and stomach.

In the consideration, therefore, of sudden death we end where we began, that contrary to the beliefs of both the medical profession and the laity, sudden and unexpected death is but rarely produced by cerebral hemorrhage. The great majority of sudden unexpected deaths occur in certain forms of heart disease, but the overwhelming majority of deaths in heart disease are neither sudden nor unexpected.

In considering cardiac pain we must frankly admit that the explanations given for it, and the theories held concerning it are unsatisfactory, do not correspond with the experimental observa-

tions. Cardiac pain varies in its intensity from mild annoying precordial discomfort to the most intense forms of agony, spreading over various areas of the chest and arms. Clinically it almost invariably carries with it a sense of fear, because of the well-recognized belief that precordial pain means angina, and angina means sudden death.

Unquestionably the pain when it does occur arises from two different areas supplied by the coronary arteries, and their afferent nerves, one in the first portion of the aorta from the morbid conditions produced by aortitis, and the second is from the morbid conditions of the coronaries supplying the atrioventricular portion of the heart.

This difference in origin gives a different clinical picture to the type of pain. The aortic type corresponds to Heberden's first description, and, as you know, the pain is a substernal pain going up the chest into the throat, and at times into the jaw, and over the great occipital nerve, or else adding to or avoiding this area, going up to the left shoulder and down the left arm by the ulnar nerve to the tip of the fingers. It may, of course, begin subinternally and go directly to the left arm or right arm, or both arms.

In this symptom complex there is also a tremendous viselike pressure from the muscles of the chest, there is often a curious conviction in consciousness that death is near and there is a noticeable lack of dyspnea, with normal steady pulse, and the patient gives one the picture of a stricken animal, not daring to move, sitting or standing in agony, waiting for death to relieve him, or turning with appealing eyes for relief. In the attacks of pain in the atrioventricular coronaries the pain in about one-third of the cases follows the same line up to the left shoulder, and down the arm, the patient complaining bitterly about both pain and dyspnea, but in about two-thirds of the cases the pain is felt in the epigastrium or in the lower part of the sternum, with a shooting pain around under the ribs in the sixth and seventh nerves. The patient often complains bitterly of the choking sensation from gas, and refuses to talk to you about the pain, disregards even the dyspnea, but discusses nothing but the indigestion and the oppressive gas from which he cannot obtain relief. The pain often is so intense in the epigastrium that the patient lies like one with acute perforation of the abdominal viscera, and the diagnosis between a coronary attack and gastric or duodenal perforation is often a difficult one. Often between attacks these patients with coronary disease suffer intense discomfort from the enormous amounts of gas that they discharge, either by mouth or by the bowel.

These patients with this coronary disease also have coronary thrombosis with its familiar picture, but what is not usually appreciated, they frequently have these attacks of pain without the thrombosis. These attacks of pain of both types are often brought

on by very slight exertion, or exposure to cold, or by some vigorous emotion. Often the most intense attacks occur in patients in their sleep, with seemingly the body at rest, and only the autonomic nervous system still active.

The anginal syndrome may follow an attack of acute infectious disease as influenza, and, curiously, the substernal pain radiating down the arm not uncommonly occurs with patients suffering from pernicious anemia, and it ceases immediately after blood transfusion. Intense precordial pain is very commonly complained of by those recovering from prolonged alcoholic intoxication.

Nicotin poisoning produces precordial pain very frequently in its minor degrees of intoxication. The use of tobacco by those subject to attacks of angina increases both the frequency and the intensity of the attacks.

Clinically the exhibition of the symptom complex of cardiac pain seems to arise in so many conditions as to baffle a comprehensive explanation. The pathologic anatomy found in those who have suffered from angina seems as incongruous as the clinical picture. Those who have the aortic pain show an aortitis very frequently of a luetic type, involving also the origin and a short distance into the coronary arteries, and they may also have arteriosclerosis of nonluetic causation of the coronary arteries. Those who have the coronary type of pain show arteriosclerotic changes in the coronaries and may have normal aortas, but many patients living and dying with aortitis and with sclerotic coronaries never show any cardiac pain whatever.

Obendorfer, Kirch and Edens, in recent excellent reviews, faced with the incongruity between pathologic anatomic and clinical manifestations of pain, conclude that spasm of the coronaries is the most probable explanation of the anginal symptoms. This is the belief usually accepted by the profession; others believe that it is the ischemia of the myocardium produced by the spasm, and not the spasm itself that produces the pain. Spasm of the coronary arteries is, however, a theoretical assumption and an unproven reality.

Others still believe that the myocardial muscle must be the cause of the pain, because angina occurs in those hearts which show myocardial degeneration, and yet hearts suffering from myocardial diseases are the ones most free from pain. Wenckebach believes that in some way there is a stasis in the coronary arteries whose distention produces pain, or that the depressor reflexes causing vasodilatation may be reversed into pressor reflexes causing vasoconstriction and a rise of blood pressure. Allbutt believed that anginal pain was due only to nerve endings in first portion of the aorta, that the coronary arteries had nothing to do with the pain but a great deal to do with the cause of death. Danielopolu believes that the metabolites of muscular action poison the heart

sufficiently to produce a cardiac failure and give pain. Pauli, in Vienna thinks it must be some lack of equilibrium between the two portions of the autonomic system. It is evident, therefore, that there is no definite agreement as to the cause of cardiac pain.

The operation of sympathectomy in recent years has helped to clarify the situation, in that it has shown that several different operations on the sympathetic and vagus systems have succeeded in stopping the attacks of pain, but no one operation has been always successful. It shows, therefore, that either different nerves vary greatly in different individuals in the transmission of their physiologic function, or else the breaking of the continuity of reflex action is equally effective as the cutting off of afferent sensory fibers and pathways.

The results of sympathectomy also indicate strongly the necessity of separating in ones clinical picture the pain of aortic origin from that of other coronary fields, since operations successful against the pain of aortic origin have failed in other patients when the pain arose from the atrioventricular coronaries. It has also become increasingly evident that in certain conditions in which the atrioventricular coronaries are involved sympathectomy not only is unsuccessful, but is distinctly contraindicated.

The morbid conditions found in aortitis in those giving a history of anginal pain are, according to Kutchera Aichbergen, that the adventitia of the aortic wall is adherent to the muscular media at the inflamed areas in the wall of the aorta, the wall being thinned at these points. The morphologic conditions for a sudden distention are, therefore, present, and the severest strain is to be expected exactly on the inflamed areas. It is in such cases as these that we find a previous history of angina pectoris, especially if the aortic valves are thickened or the coronary openings are narrowed or closed.

In aortitis the coronaries are often involved only near their mouths, or are entirely normal. It is difficult, therefore, to understand how the coronaries should be contracted in spasm, especially when they are protected from the thrust of the blood by either stenosis or by closure, and more especially still when their mouths are open by the fact that at each systole of the heart the coronary circulation is blocked by the contracting myocardium and the inflow only occurs during the relaxation of the diastolic period.

When there is much scar tissue, or calcified infiltration of the aortic wall, or in cases of large stiff walled aneurysm, the history of anginal pain is usually absent. Anginal pain occurs in thin walled mycotic aneurysms, and with ruptured aorta.

In arteriosclerosis of the bloodvessels, from whatever cause it arises, the first tissue to become involved is the internal elastic tissue. This breaks down, and is followed in the areas so affected by the thickening of the intima, which, according to Thoma, is a protective reaction in defence of the stretching muscularis.

Kutehera Aichbergen emphasizes the fact that with these thickened arteries, and with the calcified arteries, the anginal pains are less common, unless coronary thrombosis or coronary infarct has occurred. But with the distended walls frequently seen in the coronaries of those giving a history of angina pectoris all the tissues are thinned out and stretched, the muscularis is not hypertrophied as it would be from constant exercise of spasm and the internal elastic layer is often completely smoothed out, not normally folded like a neck ruff, and these changes can only be explained by the stretching of the internal elastic layer. It is this type of artery that is particularly prone to seizures of pain.

But after all, pathologic anatomy can only show how far at death the tissues had changed from normal, and perhaps what normal functions were inhibited during life. It often shows why certain symptoms occurred, or why at times the processes necessarily ended in death. It does not explain the functional reflexes which give rise to angina pectoris.

The more we study the clinical picture of angina pectoris and cardiac pain, the more are we forced to realize that the explanation lies in the normal anatomy of the vegetative nervous system, and in excessive function or perversion of the normal physiologic reflexes by which the heart and its own vascular system respond, or fail to respond, to the demands made upon them by the rest of the body through the circulation. In normal healthy athletic youth the heart responds instantly with unlimited power to all bodily demands, but as the hardiness of youth passes and bodily vigor declines, or sloth degenerates it, the heart loses its power for instant call, and although it may regain this power for a time through work and persistent repetition of its functions, there comes a time when senescence begins, when the heart and its vascular system are permanently damaged and it has lost its power to act and lost the ability to regain its former functional vigor. It is in this period of senescence in the fifties and sixties that angina usually occurs. Angina does not wait for the rigid calcified deposits of senility; it may well occur earlier. Syphilis demands its reckoning even in middle life, and Mönckeberg has shown that nonluetic arteriosclerosis of the coronaries frequently begins in early manhood, as youth is ended, and the descending branch of the left coronary is often the first artery in the body to be affected. Degenerative tissue, either cardiac or otherwise, cannot perform the vigorous functions of normal tissues, and either by failure to perform their functions, or through failure to prevent excesses, such as over-distention or stretching, excessive reflexes are set in motion. These produce the sensation of pain, and upset the smooth performance of the functions of other viscera, and we have the symptom of angina pectoris. Let us see now if the facts bear out this assumption, and if the normal anatomy and normal reflexes of the heart justify us in thinking in terms of the above statement.

All are familiar with the intricate anastomoses between the three sympathetic cardiac nerves in the neck and the three branches of the vagus going down to the cardiac plexus. Ransom has shown that above the middle ganglion of the sympathetic cord the afferent fibers carrying pain do not go. In the superior cardiac nerve go the pathways for transmission of the vasomotor reflexes. Arising from the aorta there is a nerve which usually has also a branch from the sympathetic system, and which goes up through the vagus and by a branch to the superior laryngeal nerve, or to its external branch. This is the depressor nerve which carries afferent impulses to the medulla, causing a lowering of blood pressure when the pressure becomes too high in the aorta, and it does this through stimulation of the dilator center, causing a general fall of blood pressure. The afferent nerves carrying pain from the heart and aorta go out through the inferior cardiac nerve, and the middle sympathetic nerve to the eighth cervical ganglion, and the first thoracic, or to the combined stellate ganglion, and also down to the five upper thoracic ganglia, going into the cord through the posterior roots of these spinal nerves.

There are also nerves in man, as shown by Braücker, Jonesco and Morehouse, going directly from the thoracic ganglia even as low as the seventh dorsal ganglion, without going through the main sympathetic cord up to the stellate ganglion, but which pass directly over to the lungs and the heart through the pulmonary and cardiac plexus. These carry accelerator fibers and also afferent fibers. The accelerator sympathetic fibers go up through the stellate ganglion from the upper thoracic nerves, and go through the inferior and middle cardiac nerves and from the loop of Vieussens to the heart. The afferent nerves coming from the heart pass out to the cord by the rami communicantes through the ganglions on the posterior nerve roots and in the cord they go up the spinothalamic tracts of the cord to the thalamus and thus ultimately reach the sphere of consciousness.

In the heart itself Woolhard has shown that the ordinary ganglia of the heart, which are so abundant around the great veins and on the auricles, belong to the vagal system, and are the ganglia which send out the postganglionic fibers of the vagal system. While the auricular and atrioventricular bundle are supplied by both systems, the ventricular muscles are apparently supplied by only the sympathetic nerves. The sympathetic fibers arise from the various ganglia in the main sympathetic trunk, and come to the heart as postganglionic fibers. Woolhard has also shown that on the main branches and arterioles of the coronary system the sympathetic fibers predominate, but the vagal fibers predominate on the arterioles and capillaries on the heart muscle. Anrep and his coworkers have brought forward strong evidence to show that the sympathetic nerves are the vasodilators of the coronary arteries and the vagus

nerves are the vasoconstrictors. It is important also to remember that the blood supply of the first portion of the aorta is only from both coronary arteries which form the *vasæ vasorum* of this portion of the aorta. The sensory nerves of the aorta and of the coronary arteries lie in the adventitia. The sensory nerves of the heart, therefore, lie in the adventitia of its bloodvessels, and to account for cardiac pain we must turn to some cause of nervous reaction to the nerve endings of these sensory nerves in the adventitia of the aorta and of the coronaries. Odermatt, in studying the sensitiveness of bloodvessels has clearly shown that some arteries are sensitive to ligation, small arteries more so than large ones, for example, the radial more so than the brachial, and he also, with Dogiel, proved that the sensory nerve endings of bloodvessels rested in their adventitial coat. Odermatt also found that arteries which were sensitive to ligation were also sensitive when their adventitia was stretched or distended, that is, stretching or distention of these same arteries produced pain. That it was by distention and not by contraction that pain arose. There is no evidence that arteries have colic in the same manner that intestines do.

Singer has demonstrated that an acute ischemia of the cardiac muscle is without any painful reaction in the experimental animal, and that the chemical and mechanical insults causing pain in the pericardium, epicardium, aorta and coronary vessels do not excite pain in the cardiac muscle. The pericardium is distinctly sensitive to mechanical and chemical irritation, but Faradic irritation provokes hardly any reaction. The epicardium is insensitive to electric, but sensitive to mechanical and especially to chemical irritation. The endocardium and the cardiac muscle were completely refractory to the above three forms of irritation. The sensibility of the coronary vessels is conditioned on the intactness of their adventitia. This portion of the aortic wall possesses a strong mechanical and chemical sensibility, but sensitiveness to pain on the part of the media and intima could not be demonstrated.

The aorta was but feebly sensitive to Faradic irritation. It is only mildly sensitive to chemical inflammatory irritations, but to mechanical irritation, such as pinching and pulling and stretching it was strongly sensitive. Here also the sensibility depends on the anatomic intactness of the aortic adventitia.

Spiegel and Wassermann have shown that at times stretching of the aorta produces pain; and that pain from the aorta follows the same pathways as pain from the heart. Jonesco and Singer have shown conclusively that only sympathetic fibers carry pain. There are no sensory fibers for pain in the parasympathetic nerves nor in the depressor nor in the vertebral nerves.

Singer showed that eradication of the stellate ganglion on the left side made the aorta and the left side of the heart insensitive, the right side of the heart was still slightly sensitive, the eradication



then of the right stellate ganglion made insensitive all cardiac and aortic tissues as far as the subclavian arteries.

Considering the coronary circulation, Anrep and his coworkers have found that the coronary outflow through the coronary sinus occurs in three waves—the first due to auricular contraction in presystole, the second, the smallest, is synchronous with the isometric period of ventricular rigidity, and the third, and largest, is synchronous with the ejection phase. During diastole the coronary outflow diminishes gradually, or very often abruptly, it may stop or continue. The minimum outflow, however, is always during the second half of diastole, unless the outflow is distorted by the auricular wave. With the closure of the aortic valves, the inflow begins and increases rapidly, then more slowly, and then increases constantly until the maximum of the inflow is reached, as systole begins. The coronary inflow diminishes rapidly during systole, reaching its minimum at the end of systole.

In the denervated heart aortic pressure is the only mechanical function determining coronary flow. In the denervated heart changes in the cardiac output and changes in the heart rate within wide limits and changes in strength of contraction have no direct influence on the coronary circulation, because the internal reflex mechanism is abolished.

According to Anrep and Segall, in the enervated heart, however, the coronary flow is extremely sensitive to changes in the output from the heart, although the arterial pressure still remains the chief factor influencing the coronary circulation.

The augmentation of the coronary flow and the acceleration of the heart, though simultaneous, are independent effects whether the heart is artificially stimulated to increase its rate or beats naturally with the Bainbridge reflex in play. This reflex being that an increased venous pressure on the nerve fibers in the right auricle restrains the vagus action and allows the accelerators to increase the heart rate. Anrep and Segall's coronary reflex is also of great importance, this reflex being that with an increased cardiac output, and, therefore, a greater performance of work by the heart there is an increase in the coronary blood flow. This reflex is abolished when the vagi are cut. The same rise of blood pressure produces a much greater increase in the coronary flow when the output of the heart is large than when it is small, thus reproducing the circulatory conditions in muscular exercise or in the condition of a simple increase in arterial blood pressure.

Anrep and Segall's experiments strongly indicate the existence of vasoconstrictor fibers in the parasympathetic nerves; these vasoconstrictor fibers are in a state of partial tonic excitation. This coronary reflex enables the heart to regulate its own blood supply, not only in proportion to an increase in the arterial resistance, but also proportionately to the venous filling of the ventricles. This

coronary reflex must play an important part in the circulatory conditions observed in muscular exercise, enabling the heart to adapt itself to increased demands while safeguarding its blood supply. Anrep further noted that a rise in cerebral blood pressure slightly diminished, and a fall increased the coronary flow.

Beginning with the reflexes occurring in the early stages of muscular exercise, since it is the sudden call to slight exertion as walking against the wind or up a slight grade which are often the earliest actions to inform a patient that his heart can give him pain. The first reflex at the beginning of exertion is probably that from the higher nervous centers which quickens and deepens the respiration.

This starts the necessary supply of increased oxygen, and with the bellows effect of the chest increases the venous flow into the heart. As the skeletal muscles contract, further increase of blood goes to the heart through the big veins, and there is a rise of capillary and venous pressure, and there occurs in the right auricle a vagal reflex on the nerves around the great veins as the increased blood distends the auricle; the vagus is reflexly depressed and the accelerators are stimulated so that the rate of the heart increases in proportion to the venous return, and the blood is hurried on through the heart. The increase of the  $\text{CO}_2$  and lack of  $\text{O}_2$  also accelerates the heart. The anoxemia also greatly increases the coronary flow. There is a simultaneous rapid rise in arterial pressure, and as the blood pours into the ventricles there is a stretching of the myocardial muscles, with an increased output per beat of the heart. Both this rise of aortic pressure and increased cardiac output equally increase the coronary flow through the action of Anrep's coronary reflex by the inhibition of the vagal vasoconstrictor fibers, producing capillary and arteriolar dilatation with increased coronary flow. The rise of the  $\text{CO}_2$  tension and the H-ion concentration of the blood also adds to the increase of the coronary circulation. In normal vigorous cardiac contraction the coronary vessels are compressed and emptied; during each beat of the heart the coronary circulation varies between practically emptied vessels and well-filled flowing circulation. But with the breaking down of myocardial contraction from degeneration of the muscles, with increasing blood from exertion, and with the anoxemia increasing coronary flow, and the myocardial muscles stretching to increase their action to produce increased output, the degenerated muscles cannot sufficiently contract, and the heart is in the condition of dependence for its coronary blood supply on increase of blood pressure. The degenerated muscle cannot contract vigorously enough to empty out the heart nor its own coronaries, nor can the heart increase the vigor of its contraction. For a time its increased rate per minute may act as a substitute for increased output per beat, but there comes a time when with the incompetent cardiac muscle there occurs an increasing congestion and finally dilatation of the

coronaries by which stretching of the adventitia is produced from overdistention of the diseased arteries, and pain is the result. This pain comes from the coronary vessels, and pain occurs until the coronary circulation can recover itself, through increased muscular action of the myocardium, or diminished inflow of blood into the heart brings relief.

All these circulatory reflexes do not necessarily act when pain arises from the aorta. With an aortitis and diseased wall, as we have shown, where the adventitia and muscularis are adherent together, or the inflammatory conditions in the vasa vasorum of the adventitia cause morbid conditions to arise, which press on the sensory nerve endings, with the increase of blood pressure in the aorta, which emotion may cause, which increased exertion causes, then there is an increase of the stretching of the aorta sufficient to produce pain, but not sufficient to cause reflex actions of the depressor nerve to occur, and bring about a cessation of this stretching. The giving of nitrite of amyl instantly produces a relaxation of the muscularis, of all bloodvessels and a fall of blood pressure and the painful stretching ceases. The action of the nitrites is substituted for that of the depressor nerve.

Summarizing briefly, it is evident, therefore, that the sensory afferent nerves of the heart and aorta originate and run in the adventitia of the first portion of the aorta and of the coronary arteries and belong only to the sympathetic systems of the autonomic nervous system. Stretching and overdistention of these vessels is brought about by normal circulatory reflexes which in diseased tissues cause excessive stretching of the aorta before the depressor reflexes bring relief or by overfilling cause overdistention of arteriosclerotic walls of the coronary arteries. As long as the circulatory reflexes do not upset the equilibrium between the myocardium and its bloodvessels there is no pain. When, however, the afferent functions of the nerves are adequately disturbed, or the myocardium so degenerated that it cannot under reflex stimulation contract normally, the normal increased rise of blood pressure and the circulatory reflexes produce excessive dilatation of the diseased bloodvessels and pain results when the heart endeavors to answer the demands for increased work.

This theory also explains the various clinical exhibitions of pain in coronary infarcts and thrombosis; if they are in small vessels local overfilling proximal to the infarct of the coronary vessel is sufficient to give pain. This also can be the cause of pain in infarcts from large vessels, but there is also added when large infarcts occur the sudden diminution in contractile power in the myocardium, and there are present two causes for overdistention and stretching of the adventitia of the coronary vessels. Probably with the intense fall of blood pressure occurring with infarction the pain is chiefly due to the stretching of the adventitia of the coronary vessels at

the proximal side of the infarct. Pain will probably not occur even in cardiac infarct if there is by chance sufficient collateral circulation to draw off the blood and prevent the coronary distention.

This theory here offered accounts for the fact that in some operations of sympathectomy, even with none of the sensory fibers cut or disturbed, the attacks of pain may entirely cease when the continuity of reflex action is prevented, and the rise of blood pressure does not take place, and on exertion the adventitia of the aorta is not overstretched to give pain. In those odd cases of pernicious anemia in which the symptom complex of angina occurs, we start with an overdistention of the coronary vessels, because the anemia itself may augment as much as six times the normal amount of the average coronary flow. With an anoxemia the myocardium cannot normally contract, and there arises a failure of the myocardium producing the coronary stasis in diseased arteries. With a blood transfusion the anemia disappears, the anoxemia vanishes, the myocardial contracting power returns, the coronaries are not overdistended and the pain ceases.

In the poisoning by nicotine the action of the drug is at the synapses in the sympathetic ganglia, with the paralysis of the postganglionic fibers. This means that the accelerators are sufficiently poisoned to inhibit the contracting and conducting power of the ventricular muscle, for, as we have shown, the accelerators preside over these functions of the ventricle, and Woolhard has shown that the ventricular muscles are supplied only by the sympathetic fibers. Here there is a toxic nervous paralysis of the ventricular contraction in place of lack of force through degenerated muscle. When the intoxication is removed the contractile power of the myocardium improves the coronary circulation and the pain ceases.

This theory is offered after many years of clinical observation and many years of puzzled study. It does explain cardiac pain logically, and is borne out in each of its separate factors by experimental work in physiology and by known anatomy, and explains the baffling incongruous clinical symptoms and pathologic anatomy found in those hearts which have given pain through their functioning existence.

**Summary.** The most frequent cause of sudden death is not cerebral hemorrhage, but some cardiac lesion. Sudden death is not of common occurrence in heart disease when all forms of heart disease are considered.

Pathologic anatomy does not offer an explanation of cardiac pain.

Experimental evidence strongly indicates that the myocardial muscular tissue is insensitive, and does not cause pain by ischemia or failure of action through anoxemia or degeneration.

Cardiac pain is expressed only through the afferent nerves of the sympathetic portion of the autonomic nervous system.

Cardiac pain occurs when functional failure of normal reflexes produces conditions which stimulate the afferent nerve endings in the adventitia of the aorta and coronary vessels.

Experimental evidence also strongly indicates that vascular distention is the usual cause of cardiac pain rather than vascular spasm.

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## CONCERNING CERTAIN PHASES OF ANGINA PECTORIS BASED ON A STUDY OF 350 CASES.\*

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I SHALL not attempt fully to discuss angina pectoris nor even attempt to consider all its most important aspects, for it is quite impossible for me to give an adequate discussion of this increasingly important syndrome in 1 hour. I have, therefore, chosen rather to present to you for thought and consideration only certain phases of the problem which have particularly intrigued me in my study of these cases in my hospital and consulting practice during the past 5 years. Much, if not most, of our opinions in regard to this fascinating condition are now undergoing very rapid evolution. I am also very far from believing that my present opinion in regard to any aspect of the problem is final or satisfactory. The subject is of more importance since the syndrome is undoubtedly rapidly increasing in occurrence and, directly or indirectly, it covers a very considerable part of the great problem of circulatory disease with which the medical profession is now so industriously concerned. Lambert says that in 1924, 22 per cent of the deaths in New York City were from cardiac disease, 2.5 per cent were of angina pectoris.

It is obvious that angina pectoris is not a disease entity but rather a symptom complex caused by at least several different pathologic states. Yet this picture is so definite in its appearance and so characteristic and dramatic a clinical entity, so very important a problem in every respect, that we should not, in my opinion, attempt to displace the term by anything more definitely allied to a more specific pathology.

The condition is always a serious one in which great disability and frequent death occurs. Ordinarily both its onset and its termination are of such a tragic type I am sure that most of us share with the intelligent laity a most wholesome fear of it. A constant menace of sudden death should always be conceded, and often this termination is of such an unheralded character that both physician and layman are always seriously impressed with the diagnosis. We

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are none the less more and more coming to realize that many cases, even severe instances of the syndrome may persist for years without causing either death or great disability. It seems to me also that our better understanding of the condition has led us to so treat it and to so manage our patients who are sufferers from it that they may in not infrequent instances occasionally live long, successful and useful lives even though subject to the condition. I feel that as we come to understand better not only the disease but also the individuals who suffer from it, we are able to offer a much more cheerful prospect to the sufferer. If we sufficiently individualize treatment we are much more likely to give relief as well as a prolonged and not inconsiderable period of worthwhile life and efficiency. Most of us can now cite unmistakable instances in which complete relief, even "cure" if you like, has been effected.

I think that all of us will admit that the condition is now much more frequent than was the case in the not remote past. Twenty or 30 years ago the disease was relatively rare in the so-called hospital classes. I have an explanation to offer for this fact, one other than that of better diagnosis of the complex. A few years back it was considered almost as a disease of the intelligent aristocracy, and as particularly of great frequency among our own and other professions, a disease of the "intelligentsia," if I may so say it. This distinction, in my observation, no longer pertains. I am finding angina frequent in my wards at Bellevue Hospital, which is one that caters I may say exclusively to the most unfortunate classes of our people. In my analysis of these cases at the hospital I have found almost without exception the disease associated with worry and great stress of life. These features are no longer confined to the so-called brain worker. Every class of society is now living lives of great and increasing emotional stress. The obligatory demand presented to every person, physical or brain worker, is for more speed, greater production and greater stress in every relation.

The statistical data which I have utilized in the preparation of this paper have been taken exclusively from my private consulting practice. Of the series of 350 cases studied 75 persons, including most of the women, were engaged in domestic occupations. But 19 were physical laborers, including policemen, soldiers, firemen and the like. Thirty cases were of the learned professions, 15 were engaged in artistic callings, 8 were financiers, 3 engineers. Fifty patients occupied executive positions and 93 were engaged in business ventures. This list suggests, of course, an increased occurrence among executives and business men. As in all lists of this kind, the decisive ratios are largely influenced by the preponderating character of the clientele which comes to any particular physician.

It is my impression that the complex is of growing occurrence among women, due, perhaps, to the increased stress of life to which

they are obligated by the modern vocations of women. Osler reports of 200 cases only 44 among women. My data also show a very high preponderance of men, notwithstanding the fact that my practice is about equally divided between men and women. Two hundred and seventy-two men are recorded in my data as compared to 88 women.

The cardinal symptoms of angina pectoris are familiar to all. It seems to me that the more simple that we keep them, the better able we shall be to visualize the problem, yet I shall venture to recapitulate them for the sake of clarity of discussion. Certainly the most outstanding symptom of the condition is pain. This was the dominant symptom in my series, being present in some degree in all cases. Pain is located almost always in the precordium and is oftentimes reflected in various directions, most commonly into the left shoulder and arm, but also upward into the neck, occasionally to the right arm and shoulder, or in other instances to wide distant areas, sometimes in the region of the appendix, to the rectum, the testis or ovary, the urethra, almost anywhere. Familiar as we are with the condition, during almost any week in my hospital cases are diagnosed as acute gall bladder disease, providentially in most instances the patient is considered as too gravely ill to justify immediate operation and the final diagnosis is usually made at autopsy; but the clinical diagnosis, based on history, for the patient enters in shock, perhaps had been cholecystitis with possible ruptured gall bladder. At autopsy these cases are found to have been usually instances of coronary thrombosis. Eleven such instances are recorded in my 350 private cases. The question of the reflection of pain, a striking symptomatic feature in about one-third of my cases, has been very adequately discussed in the literature many times. I refer particularly to the text of Mackenzie, of Alexander Lambert and many others. Vasomotor shock and various evidences of vascular spasm are other characteristic symptoms of the condition; they are present in nearly every case in more or less degree.

The most interesting symptom of the entire picture, and that which most impresses me as of primal importance, is the symptom of angina, as distinct from that of mere pain. It is the most striking symptom in about 40 per cent of my cases. The anxiety, the terror which is so characteristic and almost invariably present during the attack, quite independent of the knowledge of the patient, or even of his desire to live. In physicians, absolutely unafraid of death, entirely understanding of the nature of the symptom and perhaps perfectly accustomed to it, it is just as terrorizing as to an ignorant or absolutely nonunderstanding person. This phase of the complex seems to be more closely associated with an emotional state, with a disturbance of the psyche rather than with merely a local vascular disturbance.

The condition of vascular spasm, and especially its effect on blood pressure, seems to be considered by the profession at large as associated with general hypertension. But 96 of 350 cases showed hypertension and in at least one-half of these instances the hypertension was not a result but a remote cause of the condition. On the contrary, during the actual attack the blood pressure is most commonly lower than the customary blood pressure of the individual, nor is the symptom complex, in my experience, more frequent in instances of hypertension than in those who have low pressure figures. In 200 of my cases the pressure was held well within normal limits; in 54 the pressure was subnormal. As a rule, in the attack, as in all other forms of shock, the general blood pressure is depressed during the spasm. How it may be in the heart itself, or in the coronary vessels, I leave you to speculate. This is not to be considered as contraindicating the use of the vasodilators in the relief of the attack. I have never seen the nitrites to do otherwise than give benefit even in hypotensive cases, though, as you all know, they are often useless insofar as the stopping of the attack is concerned.

Admittedly the most difficult diagnostic point is the differentiation of true cases of angina from those conditions in which angina pectoris is closely simulated by phenomena which have in themselves no serious menace. Time-honored custom has grouped these conditions under the heading of pseudoangina. I see no real reason why this term should not be preserved. My distinction, and that which I find is commonly accepted by most active clinicians, is based on prognostic values almost entirely. It is recognized by all of us that the mildness of the attack is no proper measure or essential criterion, for in many of these instances the danger to life is quite as great as in those in which the suffering is prolonged and very severe. The distinction must then be based on the presence of anatomic lesions and, to a certain extent, on etiology.

In pseudoangina anatomic defects do not exist in the heart or aorta, whereas in true angina pectoris I hold that lesions exist to a recognizable degree in practically all instances. The time and the occasion do not permit me here to enter more than superficially into this differentiation, but practically all cases of pseudoangina may be grouped under the heading of psychic and emotional phenomena. They are tremendously frequent, particularly now that the laity has become so conversant with medical or pseudomedical literature and because of the agitation which we ourselves have started for the purpose of acquainting the public with medical matters. For each true case of angina which I see, I am certain that at least 3 instances of false angina present themselves in my office. As a rule, the differentiation is not difficult, for most of those who come with the spurious article are obviously neurotics. Many of them are so well educated in the symptomatology of the



disease that their history is most misleading and difficult to evaluate until the physician becomes sufficiently acquainted with the patient to judge the credibility of his story by the character and traits of the would-be patient. Quite naturally, physicians, medical students and nurses comprise a large proportion of the cases of pseudoangina. When the physician is permitted, however, to view his patient during one or two attacks, few mistakes in differentiation will occur. The picture of angina pectoris is certainly one of the most characteristic in medicine; combine such an observation with a diligent search for lesions and with a detailed historical and physical study of etiology, and the careful physician will make few mistakes. Unfortunately, however, neurotics may frequently present possible etiologic factors worthy of full credence, and even anatomic lesions also may be present which justify the more serious diagnosis. Of course, there is no reason whatever why the pseudo case may not ultimately develop a true complex, still when one can see the attack or secure a description of it from some credible witness, mistakes will not frequently occur, especially if the case can be held under observation for a reasonable length of time, and be seen during the attack.

*Toxic angina* is another clinical picture which, in my opinion, should be carefully separated from true angina, if we are to study the disease with any scientific satisfaction. In my experience there are just three toxemias which produce a picture easily confused with true angina pectoris. They are those produced by the abuse of tobacco, coffee and tea. The first, that produced by the abuse of tobacco, or in some instances developed as a result of an abnormal sensitization to tobacco, is exceedingly frequent.

In but 4 cases of true angina under my observation has tobacco been a possible causative factor; it is a common productive factor in toxic angina. This relation is becoming more and more important since women have so widely taken up the use of tobacco, for as a class women are far more susceptible to the bad effects of tobacco than men. They are also for various reasons much more likely to carry the use of the weed beyond, far beyond, the mere employment designed to give pleasure and a feeling of content to the formation of a definite injurious habit. I am prepared, however, to admit with very few qualifications that the use of tobacco is undesirable in true angina pectoris, that it tends to augment the severity of true attacks, to increase their frequency and to greatly increase the danger. I know, however, of no authoritative study which has shown that tobacco can produce any changes in the heart muscle, in the coronary arteries or in the aorta which are capable of causing a true angina. I have never seen a case of supposed tobacco angina die, except that there were found after death lesions quite typical of those which cause angina pectoris and which cannot be produced by tobacco alone. I have seen many instances of

tobacco angina which were very distressing. I have seen patients so sensitized to the effects of tobacco that they might not enter a room in which smoking was going on without developing an attack, a clinical picture which is almost the exact counterpart of a true anginal attack, but I have never seen such a case die. Almost without exception, prompt abandonment of the drug in persons who have developed tobacco angina is followed almost if not quite immediately by a cessation of the attacks. I have seen no treatment in true angina which is so successful.

Coffee angina is much more frequent in advertising literature than in medical reports. It is not often seen in the consulting room or the hospital, but it does exist. It, too, is promptly relieved by the elimination of the drug or by cessation of its abuse. Attacks rarely proceed beyond the point of a vague, infrequently reflected discomfort or mild pain in the region of the heart. Coffee is quite incapable of causing in the heart lesions similar to those essential to the production of true angina pectoris. Most of us now employ in the treatment of angina drugs similar to or identical with the essential principles of coffee, theobromin, theocalcin and caffein. My experience leads me to feel that in those instances in which angina appears from the abuse of, or unusual sensitization to coffee, the attacks are brought about by overstimulation of the nervous system and probably, therefore, the mechanism is quite similar to that manifested in pseudoangina pectoris. I am reasonably certain also that at least some of the cases are purely imaginary, perhaps stimulated by the advertising pages of our cheaper grade magazines.

I have never seen a case of angina caused by the abuse of tea. I believe, nonetheless, that they do occur, but probably in very small numbers, save in populations which consume tea in greater abundance than is customary in the localities in which I have practised. English and Canadian colleagues have described cases to me.

In all the toxic anginas almost immediate relief follows the elimination of the causative drug. Insofar as I can determine in none of the cases are any permanent lesions developed and the only treatment necessary is abstention from the drug. Sensitization to the drugs concerned in toxic angina may often persist for long periods of time, and the sensitization may become as acute as in any form of proteid sensitization so that infinitesimal quantities of the specific drug may suffice to precipitate the paroxysm. Insofar as I can learn, there are no cases of toxic angina on record in which electrocardiographic evidence of coronary spasm or embolism has been shown. Of course, any of these drugs used to excess may produce electrocardiographic changes, but not those typical of an angina pectoris of the coronary type.

**Etiology and Pathology.** In my opinion one of the most important phases of the subject of angina pectoris is the study of its pathology and etiology. The two are indissolubly blended. It has been this

phase of the question which has most interested me during the past few years and it is the study of this portion of our problem which should lead directly to a better understanding and command of the therapeutics of the disease.

Most authors mention in this connection that there are cases of angina, even fatal ones, in which absolutely no lesions of the circulatory system can be demonstrated. So many excellent authors mention this fact that perhaps we must accept it; but always the question remains of how carefully the tissues of the heart muscle and of the coronary vessels in particular were studied. I can recall but 1 of my angina autopsies in which I was unable to find what I considered adequate lesions in the heart or aorta. In this instance, however, no microscopic studies were made; therefore, knowledge of the numerous microscopic alterations in the muscle which might exist without gross recognition and which might nevertheless be quite sufficient to cause death. From a theoretical standpoint, there is no reason whatever why spasm in otherwise adequate coronaries might not cause death, and I have no doubt whatever but that such cases may exist. As a rule, instances of vascular spasm are not limited to a single field, for example, intermittent claudication is very common in angina of coronary origin, and the occurrence of vascular spasm elsewhere should always cause us to apprehend coronary spasm as a possible cause for angina pectoris. Ten of my cases showed claudication.

The intensive study of circulatory disease of the past 10 years has crystallized our conception of the basic lesions present in angina pectoris. Most of us now agree that the typical picture of angina pectoris may be produced by any one or more of four frequent lesions. In many instances they are associated.

**Disease of the Coronary Arteries.** This may cover a very wide field. No doubt the most common lesion of the coronary vessels is an endarteritis which produces nodal strictures of the lumen. This is probably associated with a certain degree of spasm during the attack. Ordinary arteriosclerosis of the coronaries is also a very frequent change. It may occur as a part of a general process of arteriosclerosis or it may exist in very severe degree in the trunks of the heart wall with but little general involvement outside this distribution. About 45 per cent of the cases of this study were clearly of this type. Aneurysmal dilatations are seen in some cases; in a few there is an active ulcerative endarteritis, probably with the formation of ultimate thrombosis in many instances. Calcification is common, especially in old age, and periarteritis may so constrict the lumen of the vessel as to bring about attacks of angina. Finally embolism, total or partial, brings about typical anginal attacks, with the subsequent typical clinical picture of coronary thrombosis and cardiac infarction. Eighty-five of the 350 cases of this series thrombosed. All of us believe that these lesions of the coronary

vessels or of any portion of the coronary system may cause typical angina pectoris. Studies of pathologic anatomy, however, in association with clinical observations show us beyond any possible question that any, or even all, of these lesions, even complete thrombosis of the coronary vessels may exist without producing anginal symptoms. It is evident then that this pathologic anatomy is not specific to the disease. There is doubtless some additional determining factor which decides in any instance those cases which on the basis of these lesions shall produce the clinical complex and those which will not.

There are many cases of angina pectoris in which insofar as we are able to determine there are no changes in the coronaries and in which the determining focus seems to reside in the aorta. There is a possible clinical distinction between these cases; it is not a hard and fast one, but it is helpful. In the cases of coronary origin the pain reflection is, as a rule, down the arm, whereas in those instances which develop as a result of aortic lesions the pain reflection is most commonly up into the neck or is located in the manubrium sterni.

**Aortic Disease.** The changes most commonly seen in instances which originate from aortic disease are located in the conus, and in many of these there is dilatation or sacculation of the sinuses of Valsalva. That there is an intimate association and confusion between aortic and coronary disease is indicated by one of the most frequent forms of aortic disease. This is the growth of the subendothelial fibrosa, so that the inner endothelial layer is erected upward into little mounds which appear with greatest frequency at the mouths of the coronary vessels and about the openings of the vaso-vasorum. Under certain physical conditions it is readily understood why an obstruction of bloodflow into the coronary trunks is affected, so that the ultimate effect in this type of aortic disease is that of coronary occlusion or asphyxia.

Simple aortitis, cases in which the vaso vasorum are surrounded by an exudate of small round cells, cases of extensive ulceration with the laying down of fibrin clot, the strictures of cicatrization, cases in which large calcific areas and lesions are found—all these may also apparently cause angina pectoris. About 50 per cent of my cases showed aortitis of some degree or form. Again we must also confess that any or all of these gross anatomic alterations may be present without causing any symptom whatever of angina pectoris. Again it seems that we have not even here discovered a lesion specific to the syndrome, certainly not one specifically determinative of it alone, yet this is one of the most common pathologic anatomic pictures clearly causative of angina pectoris.

*Myocardial disease* is one of the most frequent causes of angina pectoris. This is a fact which is not adequately recognized by many clinicians. There may, perhaps, be some minor deviations from the

classical clinical picture of those cases of angina which develop from myocardial in contradistinction to those which appear in cases from coronary and aortic disease. Thus, for example, in these cases, as a rule, pain is not reflected characteristically into the arm and shoulder, but is more likely to be described as precordial in character, a dull aching pain usually of more constant duration than in either of the other forms and, as a rule, it is more usually developed as a result of physical stress. Unlike the other anatomic types, it is likely to be characterized by dyspnea and edema; otherwise this lesion gives practically the same picture as other forms.

The lesion in this type is very variable, depending on the origin of the defect and its chief point of location. It may appear in an acute condition, such as diphtheria, scarlet fever or other similar conditions which produce an acute parenchymatous degeneration of the myocardium. It is exceedingly common particularly after influenza, and it is not infrequent after pneumonia. It is seen also as a result of the inflammatory and degenerative process in syphilis, in rheumatic fever, acute or chronic, in which one expects to find Aschoff bodies in the heart muscle. It sometimes occurs late in the thyroid heart, in which a brown atrophy has developed. Any disease capable of setting up either a myocarditis or a myocardial degeneration may develop this type of angina pectoris. It is most commonly seen, naturally enough, in cases of fibroid heart from any cause whatever. The lesions may be, therefore, acute or chronic; some of the acute conditions are from their nature remediable, others, as in fibrosis, are invariably progressive. In those instances in which the most extensive lesion is distant from the main coronary paths, the electrocardiogram is quite different from the form most frequent in coronary cases and, of course, the electrocardiogram is that of a myocarditis and not that of coronary block.

There may be still other anatomic lesions which are capable of producing angina pectoris. It has been stated by some, for example, that certain pericardial lesions may cause the disease; this is, of course, conceivable if one assumes that the pericarditis extends into the myocardium and similarly a like process may be assumed to explain these cases which appear in association with endocarditis, either acute or chronic. Obviously in this, as in the other more frequent types of pathologic anatomy of angina pectoris, very profound myocardial lesions may exist without the least symptom or sign of angina.

When one classifies thus the pathologic anatomy of angina pectoris it is seen that its etiology must be exceedingly diversified. The extent to which this is the case has been, perhaps, insufficiently recognized by the profession.

In the *etiology* of angina pectoris I think that we must all recognize the tremendous importance of heredity. Nearly every practitioner of experience has families on his list who show a very definite

familial tendency toward the complex. It has been the most frequent manner of exitus in my own family for three generations at least. In many other instances a history of familial tendency toward cardiovascular disease is to be made out. As a rule, this is manifest in those families which develop early arteriosclerosis or who, having a natural tendency to long life from a perhaps natural degree of atherosclerosis, finally arrive at the stage of a generalized arteriosclerosis and angina pectoris. The anatomic lesions most prevalent in these familial cases is that of coronary disease, next aortic disease and last of all the myocardial lesions.

Arteriosclerosis is also independently a frequent factor causative in many instances in which no hereditary influence is to be found. In some instances, as in syphilis, lead and gout, there may be a definite cause for the arteriosclerosis evident, but in many other cases no cause may be thus apparent. It seems in very many cases that it is not the degree or type of the arterial disease but the individual peculiarity which determines whether or not the case will manifest angina. Hypertension is a factor in some cases beyond doubt; but no frequent relationship between hypertension and angina pectoris is seen in the series of cases which is the foundation of this study, though the cardiovascular-renal complex was a probable cause in several. Hypotension is, indeed, more frequent than hypertension, but it occurs as an incident and probably not as a causative factor, though Mackenzie evidently believed differently on this point.

Age alone does not seem to be a very great etiologic factor, though the syndrome is, indeed, rare except in adult life. One of Heberden's cases occurred in the second year. In this series statistics show the following:

One case only developed in a patient between 20 and 30 years of age; it was an instance following severe influenzal infection and was probably a result of myocardial disease. Ten cases appeared between 30 and 40 years, 72 between 40 and 50 years, 130 between 50 and 60 years (that period of greatest emotional stress), 101 cases between 60 and 70; 24 cases between 70 and 80 and 1 between 80 and 90 years. Age as the chief etiologic factor was noted in but 7 instances.

It has long been considered as an axiom that syphilis and angina pectoris are very frequently associated. Indeed, I too held that prevalent opinion, until actual analysis of my own cases convinced me that I had probably overestimated this factor (13 cases). Syphilis may produce all three types of lesions characteristically mentioned as productive of the complex; perhaps it is most commonly associated with aortic disease, but I have found it by no means thus proportionately causative of the syndrome. Paul White has apparently arrived at a similar conclusion.

Thrombosis or embolism is frequently found postmortem in

angina pectoris. In most instances, however, the thrombosis or embolism has apparently taken place in cases which have suffered from angina for some time previously. It is, therefore, more a result than a cause. There is also a not inconsiderable group of cases in which embolism or coronary thrombosis takes place in the course of angina and causes, instead of an increase of symptoms, an actual relief. I have already a group of some 15 cases under study in which this took place. Obviously all of these instances must have been of coronary origin, and this small group tends to emphasize the importance of coronary spasm in the induction of the clinical picture; for it is only conceivable that it is in such instances that relief of the symptoms can follow a thrombosis. It has at least been probably as effective in the cure of the syndrome as surgical measures, and while it in no way cures the disease, it stops its symptomatology very much as the various surgical procedures may do, at the probable expense of depriving the patient of the warning benefit of pain. In thrombosis there is a certain definite increased crippling of actual cardiac reserve, through the resulting myocardial defect resulting from the infarction and the adjacent myocarditis and degeneration.

Nothing can appear more obvious to the ordinary student of this subject than that the most frequently associated etiologic factor with angina pectoris is emotional stress. No other one immediate factor is so dominant in the precipitation of the immediate paroxysm and the very tendency of the disease chiefly to manifest itself in certain occupations and types of individuals is further illustrative of this fact. It is those concerned with the stressful phases of life that are chiefly affected by the syndrome, and it is during periods of emotional stresses that the initial paroxysm almost always appears. It is advanced by many that this fact in itself is a powerful argument, indicative of the arterial spasm theory of production, and this argument is further carried out by the frequency with which other spasmodic attacks of other vascular distributions appear in the same case. I wish in particular to mention the associated occurrence of intermittent claudication, abdominal anginas and the like. This association of other definite areas of arterial spasm in this disease has been observed in 81 of our series of cases.

Physical stresses as the cause of the symptom of angina is present in practically all well-established cases, the longer the standing, the more obvious does the relationship become. On the other hand, it is not those whose occupations entail great physical effort who chiefly develop the disease, but quite the contrary. Physical stress then should be considered not as a productive factor, though in established cases it is one of the most frequent immediately causative agents insofar as the individual paroxysm is concerned.

**Diagnosis.** It is not my purpose here to attempt to discuss diagnosis in any detail, for the reason that I think it far easier to make

the diagnosis in the individual case than to lay down hard and fast lines for diagnosis theoretically. My experience as a consultant has been that the average physician, surgeon, obstetrician or pediatricist is usually fully informed on this phase of the subject, and I do not believe that it requires any special consideration; but there are a few factors which my experience has led me to wish to emphasize on this question of diagnosis.

Obviously the chief problem is the distinction from pseudoangina which I have already in part discussed. In diagnosis, considerable attention and weight must be accorded to an estimation of the credibility of the patient on the degree and character of his pain. So many of the public are so well informed on these symptoms that they are likely perhaps unconsciously to tell a conclusive story of the disease through their very fear of it. An attractive and brilliant young woman, in her early twenties, recently came to my office with an almost letter-perfect recital of symptoms, and her suffering had become so severe that her brilliant future as a musician was seriously threatened. She almost persuaded me that she had true angina, so accurately did she describe it. Fortunately she permitted me to conduct experimental tests which I could never encourage in cases supposedly anginoid, for I exercised her to the extent of exhaustion without inducing an attack. The electrocardiogram was entirely negative. She was hypotensive, very suggestive, appallingly emotional; but absolutely no physical signs could be detected which could account for a basic pathology. I finally submitted her to very distressing emotional stress which induced an attack, and the nature of that attack at once persuaded me that we were dealing with an anxiety neurosis; for the patient was voluble with her symptoms *during the attack*; she could not remain at rest, but walked back and forth in the examining room; there was no cardiac arrhythmia—she was evidently in severe distress, but definitely not from an angina. A frank statement backed with a lack of all contributory pathologic anatomy finally succeeded in persuading the young woman that her attack was purely an emotional reaction and accompanied by no danger or real cardiac disease. She has had no subsequent attacks, and I confess that I have been much relieved also, for she nearly had me persuaded that she really had an angina.

The point is that observation of the attack is the most highly diagnostic fact. In my opinion the second most important fact is the determination of an adequate pathologic foundation. A failure to obtain some degree of amelioration under the nitrites is a strong negative point in difficult diagnosis. Always the elimination of emotional and hysterical states is a difficult matter. In some instances, of course, a knowledge of the personality of the patient is absolutely necessary in this respect and such an evaluation is always of great assistance in diagnosis.



There can be no question as to the high value of the electrocardiogram in the diagnosis of angina pectoris when it furnishes positive evidence. Negative electrocardiographic findings are of no value however either in a positive or a negative way. Frequent observers have reported entirely negative electrocardiographic findings even when taken in the height of the attack. Three such instances have fallen under my own observation, and in all the diagnosis was subsequently fully established—in 2 instances by death and in 1 by autopsy. Neither are electrocardiographic findings constant. In a recent case seen by me in consultation with Dr. Rabinowitz, of the Brooklyn Jewish Hospital, during a quiescent phase the electrocardiogram showed an absolutely positive picture, but during an attack 2 days later the record obtained by the same technician with the same instrument indicated absolutely no abnormality. This case was confirmed in diagnosis by an extensive coronary thrombosis a few days later.

**Treatment.** In many ways the most interesting subject in our present-day study of angina pectoris is that of treatment, and such is the importance of the subject that it warrants considerable discussion.

The question is frequently asked both by the physician and layman, Can angina pectoris be cured? In the past it has been largely the custom of many of us to answer such a question with the statement, "Only in cases of mistaken diagnosis." Our study of the pathology of the complex, however, in the past few years, associated with clinical observations which permit of little opportunity for error in diagnosis has led us to the answer that angina pectoris can be cured in instances in which the basic fault can be rectified. Obviously those cases founded on coronary and aortic lesions are the most difficult of cure in this regard, but many of the cases in which the basic fault is located in removable or curable lesions of the myocardium can certainly be cured.

I have seen cases caused by syphilis, believed to have been based on coronary or aortic lesions, which apparently underwent complete cure, though even in these most favorable instances there was in all probability some definite subsequent limitation of cardiac reserve nonetheless. Many cases presenting quite characteristic clinical pictures, and a few with electrocardiographic positive evidence in which the basic fault lies in the myocardium, become apparently cured. I speak particularly of instances which arise after the acute infections, especially after influenza, pneumonia, tonsillitis and the like. Some cases apparently of rheumatic origin also have appeared to improve to the point of practical recovery, though almost if not always with some subsequent limitation of cardiac reserve. I am certain that we have permitted the lay public to become convinced of our undue pessimism in regard to this disease, and our pessimism has led in many cases to ineffective treatment on the

part of the doctor and inefficient coöperation on the part of the patient. My optimism, particularly in regard to syphilitic cases, I find has led me to be misquoted in some instances. Because early and efficient specific treatment will cure early cases of luetic angina pectoris in many instances, clinicians have concluded that any case due to syphilis should be cured. This is, of course, very far from the truth. When fibrosis has taken place, either in the heart muscle or in the walls of the coronary or aorta, it is not to be expected that cure, which is obviously dependent on removal of the underlying lesion, can take place, though it is perfectly true that in a very high percentage of these cases great benefit symptomatically and not infrequently a staying of progress can be effected, one can never tell except by therapeutic experiment.

Disappearance of symptoms is very frequent, and it occurs in very many instances, particularly if the treatment is properly administered and introduced before grave tissue changes have taken place. Disappearance of symptoms, however, is usually associated with a degree of permanent cardiac disability.

I have seen apparent complete relief follow in 2 cases probably caused by gout. Both signs and symptoms entirely disappeared under proper diet and medication. A few cases of what I took to be true angina pectoris have received symptomatic cure from the relief of secondary subsidiary factors. Thus I have seen symptoms subside from the giving up of tobacco, the cessation of violent exercise or from a better control of the temper. It is most important in the treatment of individual cases to take all these factors into full consideration.

Discussion of treatment resolves itself naturally into the treatment of the underlying disease and that of the paroxysm. The former is, of course, the more important; but primary effort is to give relief to the acute attacks and insofar as possible to prevent the onset of others. I am convinced that there is such a thing as an anginal habit, *i. e.*, that one attack predisposes to another, and if attacks are never allowed to eventuate or to come to a climax there is a definite tendency toward less frequent attacks, the habit tendency instead of increasing, as is usually the case, becomes lessened. For this reason I think it important that the patient should promptly use his nitrite or such other measures as may be efficient in preventing the development of the complete attack. Rest, elimination of tobacco, attention to abdominal distention, a diet suited to the particular case under study, thorough emptying of the bowel and especially control of the emotions should be practised insofar as possible. In this regard, there is a well-known fact infrequently mentioned in the literature, but exceedingly important and well recognized by most clinicians, namely, that sexual excitement is exceedingly inadvisable in these cases. The number of cases which die under such conditions is large.

It is hardly necessary to enter closely into the discussion of treatment of the acute paroxysm. The best methods are well recognized; there are few but most insistent demands and the drugs which we have at our disposal are not numerous. The one drug which will give the most relief in severe attacks is morphin. I have seen instances so severe that as a humanitarian measure, I gave chloroform. I have never had a patient die under the drug, and I believe that it is justifiable in some instances. Morphin will usually suffice, but it must be given courageously. Very recently I saw such a case which had been under chloroform for several hours; recovery followed.

Many attacks are immediately relieved by the nitrites, either the inhalation of amyl nitrite or by the taking of nitroglycerin by mouth or by hypodermic. There is nothing in the theory that nitroglycerin acts more quickly when given by holding it under the tongue than when it is swallowed. The liquid preparations of nitroglycerin are usually more efficient, and it is wise for the patient to carry in his pocket a small phial of spirits of glonoin freshly prepared each day for emergency use, unless perchance it has been found that the tablets, usually hypodermic ones, are equally efficient. When the ampules of amyl nitrite are found effective they are perhaps most convenient, but they are usually not so prompt in effect as nitroglycerin. Even in the management of these acute attacks you will find that a singular amount of individual peculiarity exists, and it is well worth while to try to study out these special reactions so that your patient may always receive the maximum benefit as promptly as possible. Of course, when coronary embolism occurs a special line of treatment, which involves the liberal use of morphin, chloral and profound rest, must be instituted.

When the paroxysms are very frequent and severe, confinement to bed is advisable, at least until it can be experimentally determined that the attacks are not decreased by this measure. There are unquestionably many cases which do better if allowed up about, and some at their customary occupations. In this respect, as in all others in this problem, it cannot be too insistently emphasized that individualization is absolutely essential in the treatment of this condition; it is imperative. Exercise is another matter which must be determined only by experiment. Usually it should be diminished merely to that of necessity, but there are exceptions. So great is the emotional factor in this complex that it is often better to permit the patient to do at least some of his ordinary work, if thereby he is rendered more content and happy. I have had many instances in my experience which demonstrate this point. Throughout it must be most positively recognized that in this disease emotional stresses are even more important than physical ones.

These general measures having been instituted, the next most important thing is to attack the underlying cause. In case it is

due to syphilis, specific treatment must be given, and it is inadvisable to use the arsenical preparations until the patient has first been brought well under the effects of mercury, iodid or bismuth. In case of a basic gout, colchicum, atophan and the alkalies, water and a suitable diet are to be enforced. In case the basic lesion is a myocardial degeneration, rest and the elimination of the causative factors insofar as possible are imperative requirements. The same is true of acute myocarditis, such as, for example, may occur in rheumatic fever. There can be but little doubt but that the salicylates in these instances sometimes at least effect much benefit. I have seen cases get more actual relief from the salicylates than from the opium preparations in these cases.

In fibroid myocarditis and occasionally also in myocardial degeneration digitalis occasionally gives great relief, both in relieving the severity of the paroxysms and in lessening their number. In coronary cases it gives little or no relief, and oftentimes makes the attacks more severe and frequent. It may be tested out experimentally, however. In all cases, except in thrombosis, the vasodilators are tremendously beneficial, and the nitrites, nitroglycerin, sodium nitrite, erythroltetranitrite and the like are all used successfully in the prevention as well as in the relief of attacks.

Sleep and rest are of crucial importance, and when they may not be obtained otherwise the opium preparations are advisedly, if not compelledly given. The vasodilator sedatives, led in efficiency by chloral hydrate and similar drugs, are preferably given at bedtime. Alcohol, recommended many years ago by Heberden and others of his time, has a very definite benefit in very many cases, especially among the aged and arteriosclerotic. It is a splendid preventive also. Such sedatives as the bromids, barbital and the like, may be employed habitually for long periods.

The spiritual side of the case must not be neglected in this disease in which the emotions play so important a rôle. The development of a philosophy of life, of the power of adaptation of desire to possibilities, the cultivation of hobbies of a restful character, such as suitable reading, music and such pacific occupations as painting, etching, carving and similar pursuits, are of real medical benefit. Habits of restfulness and relaxation are to be cultivated. Climate is often very important, and those who live in the temperate zones may well spend their winters in the South or perhaps go to live permanently in some mild, temperate and congenial climate. Few patients do well in the cold places or at high altitudes.

Meantime attempts at the maintenance of cardiac reserve must be made; the use of massage when exercise is impossible; a diet must be devised suitable to the particular needs and metabolic peculiarities of the patient.

If possible the patient should be seen at frequent intervals, at least until a complete and correct appraisal of the person as well as

of the disease and lesion has been made, and treatment should be adjusted to such needs, physical, mental and medical as the individual's instance will dictate. Some cases must not be kept too long in bed, but periodic times of rest in bed are very helpful.

The treatment of angina is not a hopeless attempt. If intelligently directed it will in very many cases prolong life and add tremendously to comfort and economic efficiency. A few cases you may cure.

## EXPERIMENTAL CHRONIC HYPERPARATHYROIDISM.\*

### I. METABOLISM STUDIES IN MAN.

BY J. L. JOHNSON,

AND

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SINCE the report in 1926 of Mandl's<sup>1</sup> case of osteitis fibrosa, in which the operative removal of a parathyroid tumor was clinically beneficial, a number of cases of bone disease have been reported for which overfunction of the parathyroid glands has been thought to be the underlying cause. These cases represent, for the most part, the generalized skeletal abnormality first clearly described by von Recklinghausen<sup>2</sup> and designated by him as osteitis fibrosa osteoplastica, but hypertrophy and tumor formation of the parathyroids have been noted also in osteomalacia and rickets, as well as in multiple myeloma and metastatic carcinoma. It thus was not quite clear whether hyperfunction of the parathyroids produced one sharply distinguishable disease or could be responsible for a variety of bone lesions and it seemed that the subject might be clarified by reproducing a chronic state of hyperparathyroidism in otherwise normal animals, and observing histologically and otherwise, the type of skeletal deformity which would result.

Our interest in the problem was aroused by personal experience with 2 cases of bone disease, in both of which parathyroid tumors were found. Further stimulus was given to our interest by the extensive metabolism studies of Aub and his associates<sup>3,4,5</sup> in which they injected parathormone into normal and pathologic human subjects and observed biochemical changes quite similar to those characteristic of patients with parathyroid tumors and by

\* Read before the Association of American Physicians, Atlantic City, May 6, 1931.

their animal experiments<sup>6</sup> in which they demonstrated by gross examination a loss of bone trabeculae as a result of chronic injections of parathormone.

Our aim was to provide a complete study of gross, roentgenologic and histologic changes in the bones of animals, subjected to chronic injections of parathormone, to determine whether the lesions were characteristic of one or more of the bone diseases mentioned and to observe whether the simultaneous administration of irradiated ergosterol would influence the results. Our interest in the effect

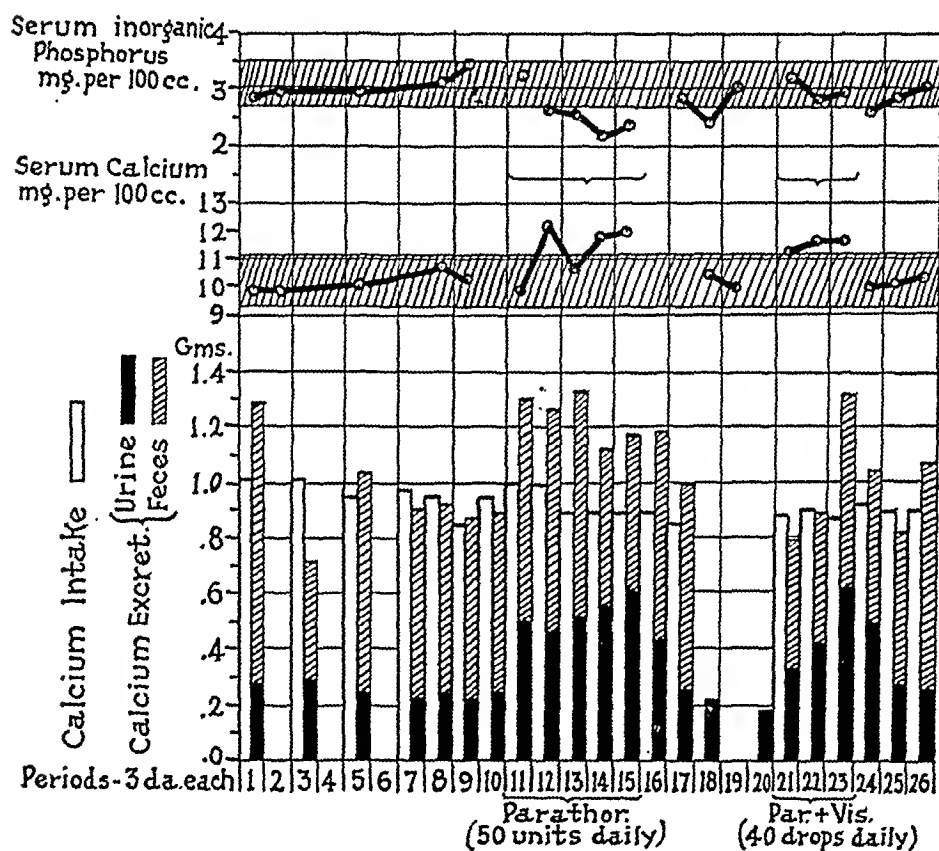


FIG. 1.—Parathormone experiment, October 14 to December 31, 1930, J. L. J., ♂, 35 years; height, 64½ inches; weight, 131 pounds.

of the ergosterol was aroused by incompletely controlled observations in a case of fibroid osteitis<sup>7</sup> which had led us to infer that the course of this disease had been favorably influenced by vitamin D, also by the fact reported by Nonidez and Goodale,<sup>8</sup> Higgins and Sheard,<sup>9</sup> that deprivation of vitamin D led to parathyroid hyperplasia. There was a hint in this that fibroid osteitis was closely related to rickets and osteomalacia.

The study was made the subject of a thesis for the doctorate of philosophy by J. L. Johnson and the details of these experiments will be reported elsewhere by him. He began them in July, 1929, and had obtained very convincing results before we learned of the

similar studies of Jaffé and Bodansky. Johnson's<sup>10</sup> observations completely confirm those of Jaffé and Bodansky.<sup>11,12</sup> The lesion produced by chronic injections of Collip's parathormone prepared by the Eli Lilly Company is a lacunar resorption of bone which involves both the trabeculae and the corticalis, and is accompanied by the replacement of both marrow and bone by fibrous connective tissue, the process including cyst formation and the appearance of giant cells, and resulting in a histologic picture that so closely resembles the generalized osteitis described by von Recklinghausen<sup>2</sup>

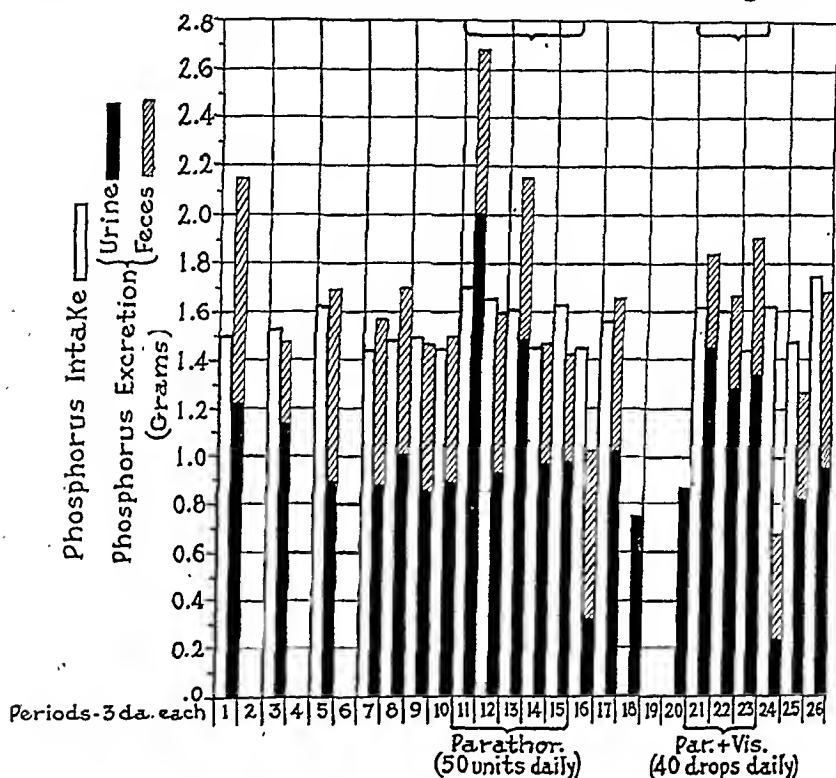


FIG. 2.—Parathormone experiment, October 14 to December 31, 1930, J. L. J., ♂, 35 years; height, 64½ inches; weight, 131 pounds.

as to be practically identical with it. No lesion has resulted, in over 100 experiments in puppies, young dogs and rats, which bore so close a resemblance to osteomalacia, to rickets, or to any other bone disease. The experiments further reveal that the effects of parathormone injections are not counteracted by the simultaneous administration of irradiated ergosterol.

The dosage of parathormone in the case of the rats was usually 20 units a day and when viosterol was added, its dose was usually 15 drops a day. In the case of the puppies the parathormone dosage was increased progressively from 2 to 20 units a day. The viosterol given to puppies was 5 to 20 drops daily. It will be recalled that the

rat has been considered to be unusually resistant to parathormone. Our experiments show that this resistance is only relative and that proper doses of the hormone are definitely active.<sup>10</sup>

Two calcium and phosphorus balance experiments were included as a part of this study. These were made on two human subjects with a view to observing the biochemical and symptomatic effects of daily injections of parathormone, and in order to discover whether these would be influenced by treatment with irradiated ergosterol. The results in one of these experiments we wish to report at the present time.

The subject was a healthy, male, colored student, aged 35 years, 64.5 inches in height and 131 pounds in weight. He was engaged

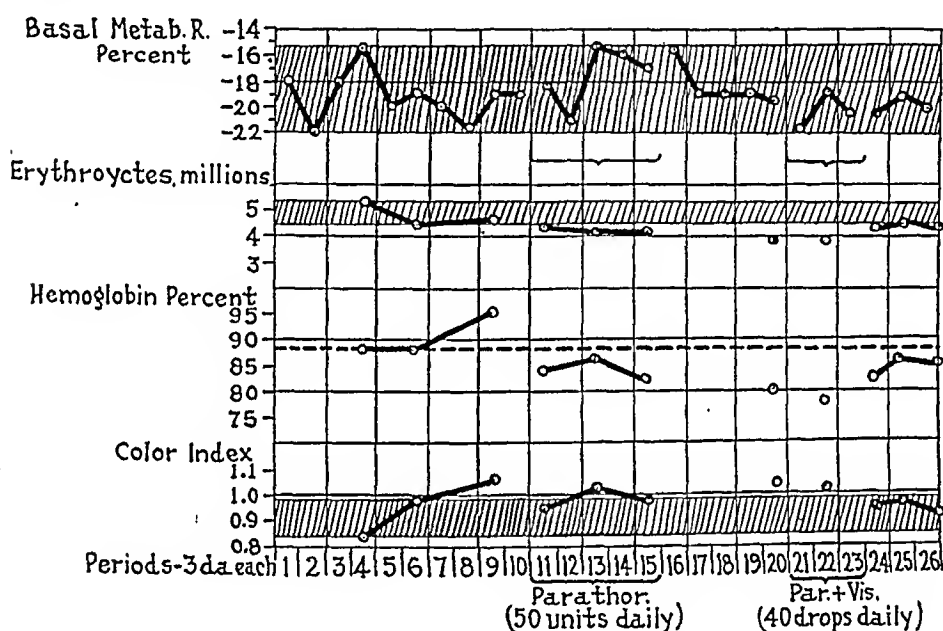


FIG. 3.—Parathormone experiment, October 14 to December 31, 1930, J. L. J., ♂, 35 years; height, 64½ inches; weight, 131 pounds.

in laboratory duties during the entire time. The technique followed in general that developed at the Massachusetts General Hospital,<sup>13</sup> differing, however, in that Bauer and Aub's diets had been rigidly limited in calcium (to about 0.1 gm.) in order to minimize the significance of unmetabolized calcium, whereas our diet was planned to contain just sufficient calcium, about 0.4 gm., to maintain a calcium equilibrium. The urine throughout the experiment was neutral to litmus, indicating a reasonable balance of acid base values in the diet. A slightly positive nitrogen balance existed throughout the experiment.

The diet was held rigidly constant for 78 days and actual control of it was maintained by direct analysis of 10 per cent aliquot portions (Table 1). These analyses were made in 20 of the 26 three-day periods. The fluid intake was held constant at 2000 cc. and the sodium chlorid at 3 gm. All water used for drinking, for the prepa-



ration of food, and for washing containers for food or excreta was distilled.\*

TABLE 1.—COMPOSITION OF THE DIET.

*Parathormone Experiment, October 14 to December 31, 1930.*

Subject: J. L. J., aged 35 years; height, 164 cm.; weight, 62.2 kg.; diet, October 21 to December 31.

Food.	Grams.	Food.	Grams.
Orange juice . . . . .	100	Butter . . . . .	55
Apple sauce . . . . .	200	Salad oil . . . . .	10
Lemon juice . . . . .	60	Egg white . . . . .	120
Sugar . . . . .	135	Steak . . . . .	40
Ginger ale . . . . .	200	Cheese . . . . .	15
Lettuce . . . . .	60	Cream, 40 per cent . . . . .	100
Celery . . . . .	30	C. P. Salt . . . . .	3
Bread . . . . .	120	Total fluids . . . . .	2000

	Calories.	Nitrogen, gm.	Calcium, gm.	Phosphorus, gm.
By calculation . . . . .	2215*	6.73	0.396	0.478
By analysis of { Max. . . . .	..	7.69	0.336	0.572
10 per cent { Min. . . . .	..	6.69	0.286	0.482
aliquots† { Mean . . . . .	..	7.04	0.307	0.522
* Basal metabolic rate . . . . .	1230			

† Aliquots of the food were prepared daily. These were combined in 3-day periods and analyzed. The diet of the entire experiment was controlled by such direct analysis.

The experiment consisted of a control or fore period of 31 days, a period of parathormone administration, in a daily dosage of 50 units, which lasted 15 days, a recovery period of 15 days, a period of 9 days with parathormone in the previous dosage plus 1 cc. of viosterol and a final recovery period of 9 days. Urine and feces were collected for analysis in 3-day lots, carmin alum markers serving for separation of the feces. The analytical methods are tabulated.<sup>13, 16, 17, 18, 19</sup> (Table 2.)

TABLE 2.—ANALYTICAL METHODS FOR METABOLISM STUDIES.

	Phosphorus.	Calcium.	Nitrogen.	Creatinin.
Urine . . . . .	Fiske and Subbarow	Aub's modification of McCrudden	Kjeldahl	Folin
Feces . . . . .	Fiske and Subbarow	McCrudden	Kjeldahl	
Food . . . . .	Fiske and Subbarow to filtrate of ash	McCrudden	Kjeldahl	
Blood serum . . . . .	Fiske and Subbarow	Clark and Collip modification of Kramer-Tisdall		

The biochemical results are shown in the accompanying charts and Table 3. The response to parathormone, like that previously reported by Collip,<sup>14</sup> Greenwald and Gross<sup>15</sup> and others, consisted of an elevation of the calcium and depression of the phosphorus of the serum, and a prompt, very markedly increased urinary

\*. The details of the preparation and serving of the diets used in this and other experiments to be reported from this laboratory, the preparation of aliquot portions of the diet, as well as the methods of collection and drying of excreta, will be the subjects of separate papers by Florence Smith, Lillian Eichelberger and their associates.

excretion of phosphorus and calcium. The data tend to support the view of Aub and his associates,<sup>4</sup> and of Albright and Ellsworth,<sup>5</sup> that the phosphorus metabolism is affected noticeably earlier than the calcium. The administration of viosterol with parathormone gave similar results except for a slight delay in the development of the maximal urinary excretions, both of phosphorus and of calcium. There was also some indication that a greater amount of both calcium and phosphorus were absorbed from the bowel. However, the effect of viosterol in this dosage was certainly not such as to demonstrate an antagonism in its action to that of the parathormone.

Daily determinations of the creatinin excretion, the nitrogen balance and the basal metabolic rate failed to indicate any metabolic alterations apart from those of the mineral metabolism. (Table 3.) A moderate anemia was observed, comparable to that reported in patients with parathyroid tumors. A very slight diuresis of short duration was observed as a result of parathormone administration.

The symptomatic response to medication with parathormone of this dosage (50 units daily) was of unusual interest. Muscular weakness appeared on the 12th day of the parathormone period. It was associated with a dull aching in, and tenderness of, muscles and bones of the arms and legs. Sharp, shooting pains followed, and a dull headache was complained of. These symptoms almost disappeared in the first recovery period but became worse than ever in the subsequent parathormone viosterol period, accompanied then by a sense of depression and loss of ability for mental work. Bone tenderness and muscle weakness were observed by Johnson<sup>10</sup> in his experimental animals. They are characteristic symptoms of fibroid osteitis.

Osteitis fibrosa osteoplastica has thus been reproduced experimentally in animals, in almost every particular, by the injection of parathormone. This convinces us of the correctness of the conclusion that the pathogenesis of this disease, as it is observed spontaneously in man, is an oversupply of parathyroid hormone. Lesions other than those characteristic of fibrous osteitis did not occur in over 100 chronic experiments with animals, from which we infer that the hypertrophies and hyperplasias of the parathyroid glands, noted in skeletal diseases other than fibroid osteitis, are secondary phenomena. The fact that viosterol neither significantly alters the disturbed calcium and phosphorus metabolism of hyperparathyroidism, nor modifies the histological abnormality of the bones of animals receiving chronic injections of parathormone, is evidence that osteitis and osteomalacia (rickets) are of different origin.

**Summary.** The repeated injection of parathormone has produced, in puppies and young rats, a uniform skeletal abnormality that is characteristic of osteitis fibrosa osteoplastica (von Recklinghausen). A lacunar resorption of the trabeculae and corticalis of bones resulted, with replacement of marrow and cortex by fibrous connective tissue and osteoid tissue. Giant cells appeared and

TABLE 3.—METABOLIC DATA IN PARATHORMONE EXPERIMENT, OCT. 14 TO DEC. 31, 1930.  
Subject: J. L. J. (Male), 35 yrs. Height, 164 cm. Average weight 59 kg.

Period (3 days each).	Calcium.				Phosphorus.				Nitrogen.				Urine.		Serum.				B.M.R., per cent.		
	Output.				Bal- ance, gm.	In- take, total gm.	Output.		Bal- ance, gm.	Output.		Vol., cc.	Cre- atinin, gm.	Calcium.		Phosphorus.					
							Urine, gm.	Feces, gm.		Urine, gm.	Feces, gm.			Max., mg.	Min., mg.	Max., mg.	Min., mg.				
I	1.018	0.274	1.021	1.295	-0.278	1.503	1.227	0.930	2.163	-0.600	20.1	22.2	2.6	24.8	-4.7	8105	4.06	10.4	9.3	2.8	-18
II	1.017	0.296	0.428	0.724	+0.293	1.530	1.142	0.338	1.480	+0.050	20.2	17.4	1.4	18.8	+1.4	6625	3.83	19.9	9.9	2.9	-22
III	0.950	0.248	0.391	1.139	-0.189	1.637	0.901	0.792	1.693	-0.056	20.4	17.0	2.8	19.8	+0.7	6310	4.16	10.4	10.0	...	-18
IV	0.978	0.233	0.792	1.025	-0.047	1.440	0.880	0.697	1.577	-0.131	20.6	17.5	2.1	19.5	+1.0	5920	4.15	...	...	...	-16
V	0.966	0.249	0.792	1.041	-0.075	1.484	0.916	0.697	1.713	-0.229	20.1	17.4	2.1	19.5	+0.3	6200	4.01	11.1	10.4	...	-20
VI	0.866	0.231	0.653	0.884	-0.018	1.494	0.866	0.598	1.464	+0.030	20.1	16.6	2.1	18.7	+1.3	5910	4.11	10.5	10.2	3.4	-21
VII	0.947	0.232	0.653	0.905	+0.012	1.454	0.899	0.598	1.497	-0.043	20.6	16.8	2.1	18.9	+1.7	6165	3.99	...	...	...	-19
Parathormone started; 25 units twice daily.																					
XI	1.009	0.500	0.800	1.300	-0.291	1.717	2.012	0.674	2.686	-0.969	21.6	16.0	2.0	18.6	+3.0	6380	4.05	12.1	10.0	3.5	-20
XII	0.989	0.464	0.800	1.264	-0.275	1.658	0.940	0.674	1.614	+0.044	20.2	16.1	2.0	18.0	+2.1	5040	3.97	12.4	11.5	2.7	-21
XIII	0.893	0.619	0.800	1.319	-0.426	1.018	1.489	0.674	2.163	-0.545	21.0	17.2	2.0	19.2	+1.9	7180	4.01	11.0	10.7	2.6	-10
XIV	0.898	0.500	0.595	1.131	-0.233	1.450	1.028	0.448	1.476	-0.020	21.0	16.7	1.4	18.1	+2.9	6390	3.72	11.8	10.9	2.6	-10
XV	0.885	0.610	0.565	1.176	-0.290	1.639	0.987	0.448	1.435	+0.204	21.1	16.9	1.4	18.2	+2.9	5930	3.82	11.8	11.0	2.8	-17
Discontinued parathormone.																					
XVI	0.893	0.436	0.748	1.184	-0.291	1.464	0.393	0.639	1.032	+0.432	20.7	16.0	2.0	17.9	+2.8	5320	4.95	...	...	...	-17
XVII	0.857	0.264	0.748	1.012	-0.155	1.571	1.023	0.639	1.662	-0.091	20.9	17.0	2.0	19.0	+1.9	6145	3.92	12.9	10.5	2.9	-19
XVIII	...	0.235	...	...	...	...	0.755	...	...	...	...	15.6	...	...	...	6190	3.08	10.5	10.5	2.4	-19
Vioosterol started; 40 drops daily.																					
XX	...	0.188	...	...	...	...	0.874	...	...	...	...	16.7	...	...	...	6465	4.20	10.0	13.0	3.0	-19
Vioosterol continued, parathormone resumed, 25 units twice daily.																					
XXI	0.890	0.337	0.472	0.809	+0.081	1.631	1.465	0.382	1.847	-0.216	21.9	10.4	1.3	17.6	+4.3	6950	4.06	11.3	10.6	3.2	-22
XXII	0.915	0.424	0.472	0.896	+0.019	1.615	1.291	0.382	1.673	-0.038	21.5	16.8	1.3	18.1	+3.5	6945	3.88	11.7	11.6	2.8	-19
XXIII	0.878	0.627	0.699	1.326	-0.448	1.447	1.357	0.558	1.915	-0.498	22.2	16.9	2.1	19.1	+3.2	6005	4.03	11.7	11.3	2.9	-20
Discontinued parathormone and vioosterol.																					
XXIV	0.933	0.492	0.544	1.036	-0.103	1.631	0.242	0.440	0.682	+0.952	23.1	16.2	1.4	17.7	+5.4	6415	3.84	11.7	10.2	2.6	-21
XXV	0.905	0.285	0.544	0.829	-0.076	1.483	0.836	0.440	1.276	+0.207	21.9	17.4	1.4	18.8	+3.1	6520	3.93	10.1	10.1	2.8	-19
XXVI	0.911	0.274	0.812	1.086	-0.175	1.762	0.900	0.727	1.627	+0.075	21.6	16.5	2.0	18.5	+3.1	6310	3.91	10.3	10.3	3.0	-20
* Blood drawn 2 hours after breakfast. † Only 1 determination during period. ‡ Blood drawn 6 hours after initial injection. § Blood drawn before first parathormone injection.																					

\* Blood drawn 2 hours after breakfast.  
† Only 1 determination during period.

‡ Blood drawn 6 hours after initial injection.

§ Blood drawn before first parathormone injection.

cysts were formed. The administration of viosterol together with parathormone did not modify significantly the end results.

The data of these animal experiments are reported in papers to follow. The present communication is concerned with observations of the metabolism of a normal human subject who was treated experimentally, first with parathormone, then with parathormone and viosterol. The characteristic disturbances of calcium and phosphorus metabolism produced by injections of parathormone, as well as certain symptoms, notably bone pain and muscle weakness, characteristic of osteitis fibrosa osteoplastica, were not significantly modified by the simultaneous administration of viosterol.

The results of these animal and human experiments confirm the view that the pathogenesis of osteitis fibrosa osteoplastica, as this disease is observed spontaneously in man, is an oversupply of parathyroid hormone and that this disease bears no relation, etiologically, either to osteomalacia or rickets.

NOTE.—It is a pleasure to acknowledge our indebtedness to the staff of the section of metabolism for their assistance and to thank Dr. G. H. A. Clowes and the Eli Lilly Company for generous supplies of parathormone.

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#### DIABETIC PYORRHEA.\*

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DENTAL diagnosis may be divided into two general classifications: The effect of dental disease upon the various organs of the body and the effect of diseases of other organs upon the oral tissues. Dental focalized infection, though often empirical, has by its

\* Read at a meeting of the Philadelphia Academy of Stomatology, April 28, 1931.

therapeutic results attained a recognized place in medical practice, while oral manifestations of systemic diseases are more often used by physicians than by dentists. Physicians value the strawberry tongue of scarlet fever, the bloodless mouth of pernicious anemia, the swollen, ulcerated gums of scurvy, the definite lead line of plumbism, the characteristic tongue of myxedema and pellagra, the extravasations of blood into mucous membranes in purpura and the yellow mouth of jaundice. The purpose of this paper is to touch both of these general classifications as observed in 138 cases of diabetes mellitus, and to dwell particularly upon the prevalence of pyorrhea in this disease.

The chief characteristic of diabetes is a disordered carbohydrate metabolism in which sugar is no longer properly stored in the liver and the muscles as glycogen, but circulates in abnormal quantities in the blood and finds its way through the kidneys into the urine. It is attended by dry skin, excessive thirst, marked emaciation and loss of strength. It exists in varying degrees of severity in different individuals and seems to be influenced by race, size and other factors. Unfortunate cases terminate either in gangrene of the extremities or the end comes through total failure of the body chemistry, with the tragic though merciful intervention of coma. All of these characteristics are perfectly familiar to the physician, but they are far less so to the dentist, and it is from the standpoint of the dentist that we must endeavor to approach the subject.

Prinz<sup>1</sup> has well suggested that theories as to the cause of pyorrhea should be classed as (1) salivary calculus, (2) infection, (3) occlusal stress, (4) constitutional disturbances and (5) alveolar atrophy. Diabetic pyorrhea seems to be the result of a constitutional disturbance.

Members of both the medical and the dental profession agree on the importance of eliminating oral sepsis from the mouths of diabetic patients, while some even claim that, as the oral infection subsides, the sugar is correspondingly reduced.

Another important factor in practice on patients with diabetes is the choice of time for all operative procedures. Unless the urine is free from sugar, and the blood sugar is kept within normal limits, wounds in the diabetic may fail to heal.<sup>2</sup> The use of insulin and the regulation of diet by a physician in coöperation with a dentist make it possible nowadays for these patients to have the benefits of dental surgery at any time it may be needed.

Another aspect of oral involvement in diabetes was reported by the writer in 1928.<sup>3</sup> Patients who have well-developed diabetes but have had no diabetic treatment exhibited the following characteristics: The teeth were loose; the gums were hypertrophied, inflamed and dark red, ulcerated and sometimes covered in spots with grayish areas of necrotic tissue. (Figs. 1 and 2.) This condition resembles pyorrhea, but it is not ordinary pyorrhea. It resembles Vincent's infection, but it is not Vincent's infection.



FIG. 1.—Type (1) diabetic pyorrhea. Note changes in gingival tissue.



FIG. 2.—Type (1) diabetic pyorrhea in a child.



FIG. 3.—Type (2) diabetic pyorrhea. Note extensive loss of alveolar bone

It resembles mercurial poisoning, but is not mercurial poisoning. It resembles cancer, but is not cancer. It is believed to be a clinical entity.

Patients who had had diabetes for some time and who had been kept under diabetic control presented other changes. Their teeth were firm; the mucous membrane, while soft, flabby and spongy, presented no areas of ulceration, and the gums, as a rule, had not receded, but there was extensive loss of alveolar bone, together with deep pockets with but little or no pus formation. (Fig. 3.)

About half of the patients reported at that time were edentulous. They invariably gave a history of loose teeth, tightening at times before they became so extremely loose as to necessitate removal. Without exception, they related that the looseness of the teeth was noticed prior to or at the time of the discovery of diabetes.

Two Europeans have recorded this condition, one in 1899<sup>4</sup> and the other in 1907.<sup>5</sup> Inglis,<sup>6</sup> in 1908, noted that a predisposition to pyorrhea alveolaris was probable in patients suffering with diabetes. The statement that the teeth became loose in diabetes appeared in the *Encyclopedia Britannica*<sup>7</sup> for the first time in 1877. In an excellent classification of oral manifestations of systemic disease Bloch<sup>8</sup> included diabetic pyorrhea. Ersner,<sup>9</sup> in 1925, recorded the prevalence of pyorrhea in diabetes, and stated that, while he had not collected any statistics on pyorrhea associated with other diseases, he believed it more prevalent in diabetes. Rhein<sup>10</sup> introduced this subject to the profession in 1888. In 1894<sup>11</sup> he presented a classification of "pyorrhea" as follows: (1) Pyorrhea simplex, embracing all cases of purely local origin and requiring only local treatment. (2) Pyorrhea complex, embracing that larger field of more serious disorders and graver affections. Under "pyorrhea complex" he suggested the use of the terms "tubercular pyorrhea," "anemic pyorrhea" and "diabetic pyorrhea."

Winnett,<sup>12</sup> in describing diabetes from the standpoint of medicine, reminds us that glucose flows about in the blood stream and bathes every tissue in the body, making an excellent culture medium for bacteria. Whether his statement, that the reason the bacteria thrive is that glucose is actually a culture medium, is true or not will have to be left for final determination to students of internal medicine. According to this author, the bacteria of the mouth plus the glucose solution plus small abrasions cause these patients to have pyorrhea. Their poor resistance is explained by the fact that "their tissues have no comeback." In the light of biochemistry the question immediately arises as to the possibility of the absorption of bone being due to the continual acidosis of the patient.

This present study is limited to clinical findings, which have been more or less uniform in 138 patients. (Table 1.) Fifty-four of these patients were toothless, with a history of pyorrhea, 3 did not show any evidence of pyorrhea, while the rest (81) had definite periodontal disease.



TABLE 1.—ANALYSIS OF CASES.

Total number of diabetic patients . . . . .	138
Number of children . . . . .	3
Number of adults not showing pyorrhea . . . . .	1
Number of children not showing pyorrhea . . . . .	2
Total number showing pyorrhea . . . . .	81
Number toothless . . . . .	54
Number showing pyorrhea, or giving history of pyorrhea . . . . .	135

The striking similarity of ordinary pyorrhea to diabetic pyorrhea would seem to indicate a reasonable possibility that some patients are being treated for pyorrhea when they should, at the same time, be treated by a physician for diabetes. The changes in the color, consistency, shape and character of the gums, together with the dry skin, thirst and loss of weight, certainly afford the dentist a suspicion useful for diagnosis.

**Conclusions.** 1. A study of 138 diabetics demonstrated that the oral cavities present certain characteristics in this condition.

2. These modifications of the dental tissues are so nearly constant as to constitute a clinical entity.

3. The number of pyorrhea patients who have diabetes is small, while the percentage of diabetic patients who have pyorrhea is large.

4. It is unwise for the dentist to attempt to diagnose diabetes by oral changes alone. The safest method is coöperation with a physician in making complete examinations, which, of course, include the appropriate study of the blood and urine.

5. With insulin and a controlled diet, the surgical procedures necessary to removing foci in the oral cavity can be undertaken with almost the same assurance as in the nondiabetic.

6. The elimination of these foci by the coöperation of the dentist and internist is not only safe but also may be the deciding factor in the case.

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## IMMUNE TRANSFUSION IN LOBAR PNEUMONIA.

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University and the Presbyterian Hospital.)

In previous papers, a study was made of the rate of development of active immunity in normal animals and in patients with lobar pneumonia, following the intravenous injection of pneumococcus vaccine.<sup>1,2</sup> The present investigation is concerned with the production of passive immunity in normal men as a result of the intramuscular injection of pneumococcus vaccine, and the use of their blood in the treatment of lobar pneumonia. It was thought that the combination of type-specific pneumococcus antibodies plus uninjured complement present in normal human blood might be more influential in arresting a severe pneumonic infection than the use of horse serum, particularly in Types II and III. That whole blood from an homologous species would be of greater value than serum from a heterologous species was suggested by Tillett's results on pneumococcus Type III infection in rabbits.<sup>3</sup> The blood of normal individuals occasionally possesses small amounts of protective substances against one or more types of pneumococcus.<sup>4</sup> Of 10 donors in whom pneumococcus vaccine injections were begun, 3 of them had small amounts of type-specific protective substance in their blood before injection.

**Methods.** The donors were injected intramuscularly in the deltoid; occasionally the injection was made subcutaneously, in doses which varied from 1 to 25 billion organisms. The injections were given generally at weekly intervals, in some instances twice a week, over a period of time which varied from 6 weeks to 1 year. No general reactions were experienced by the donors, except in one instance when the patient became definitely feverish and suffered from considerable malaise 12 hours later. The arm was only slightly sore to the touch as long as the dose injected did not exceed 15 billion organisms. Blood was withdrawn from the donor at intervals to test the degree of protection which his serum had for mice.

Direct transfusions were done in all cases except one, the patient receiving from 1000 to 1600 cc. of blood in 2 to 3 transfusions within 24 hours.

The preparation of pneumococcus vaccine and filtrate is described in previous papers.<sup>1,2</sup>

**Results.** Eight patients with lobar pneumonia were treated by transfusion of blood from immunized donors. Five donors were employed. The degree of immunity present in the serum of the donor which was capable of passive transfer to mice varied considerably in each case. In no individual was the development of protective substance equal for each type of pneumococcus, even though equal amounts of each type of vaccine were administered. It is also true that patients with lobar pneumonia who were injected intravenously with vaccine made of 3 types of pneumococcus did not develop the same amount of protective substance for each type.<sup>2</sup>

The following table (Table 1) illustrates the response in the donor's serum after injection of pneumococcus vaccine over relatively long periods of time:

TABLE 1.—PROTECTIVE SUBSTANCE IN DONOR'S SERUM AFTER ACTIVE IMMUNIZATION.

Donor.	Survival after injection PN <sub>1</sub> culture plus 0.2 cc. donor's serum.			Survival after injection PN <sub>2</sub> culture plus 0.2 cc. donor's serum.			Survival after PN <sub>3</sub> injection of culture plus 0.2 cc. donor's serum.		
	0.01	0.001	0.0001	0.01	0.001	0.0001	0.01	0.001	0.0001
1	20	20	20	20	S	S	40	40	40
	20	20	40	20	S	S	40	40	S
	20	40	40	20	S	S	40	40	S
Controls:	0.01	40 hrs.		0.01	40 hrs.		0.01	40 hrs.	
Dosage and	0.001	40 "		0.001	40 "		0.001	40 "	
death in hrs.	0.0001	40 "		0.0001	40 "		0.0001	40 "	
	0.00001	40 "		0.00001	40 "		0.00001	40 "	
	0.000001	40 "		0.000001	40 "		0.000001	40 "	
	0.0000001	80 "		0.0000001	40 "		0.0000001	40 "	
	0.00000001	40 "		0.00000001	40 "		0.00000001	40 "	

REMARKS. Donor received intramuscular injections of pneumococcus filtrate and vaccine over a period of 12 months at approximately weekly intervals. Donor's serum showed no protection before injection.

The first donor (No. 1) received a total of 80 billion pneumococcus Type I, 170 billion of pneumococcus Type II, and 170 billion of pneumococcus Type III organisms. He also received 24 cc. of pneumococcus Type I and II filtrate. Injections were made intramuscularly at weekly intervals for a period of 12 months. It is seen in the table that he developed no protective substance against Type I that was marked enough to be shown in the protection experiments with mice. Since the culture injected to test immunity was not carried lower than 0.0001 cc., a degree of protection that was less than 1000 M.L.D. (minimal lethal doses) would not make itself apparent. In the case of Type II, the donor's serum protected against 10,000 M.L.D., and in the case of Type III against 1000 M.L.D.

In Donor 2 who received the same amount of vaccine over the same period, no protection developed in his serum for Type I or II, and only slight protection for Type III, 10 M.L.D.

In Donor 3, after a period of 6 weeks in which 87 billion pneumococcus Type II organisms, and 127 billion Type III organisms were injected, the donor developed only slight protection against Type III, but very marked protection against Type II, namely 100,000 M.L.D.

Donor 4 was injected for a period of 7 months, at approximately weekly intervals, receiving a total dose of 110 billion organisms of each type. He developed no protection for Type II, but marked immunity against pneumococcus Types I and III, equivalent to 100,000 M.L.D.

Donor 5 was injected intramuscularly for a period of 5 months, at first twice a week and later once a week, receiving a total of 100 billion organisms of each type. He developed no protection against Type II pneumococcus, but marked protection against Type I (100,000 M.L.D.) and against Type III (100,000 M.L.D.). No reason is apparent to explain satisfactorily why a donor will not develop protection against one type of pneumococcus and yet produce abundant antibodies against two other types.

TABLE 2.—PASSIVE IMMUNITY IN SERUM OF PATIENT BEFORE AND AFTER IMMUNE TRANSFUSION.

Case No., age and sex.	Transfusion of.	Survival after injection of pneumococcus Type III culture plus 0.2 cc. donor's serum.			
		0.01	0.001	0.0001	0.00001
1 Age, 58 Female	1000 cc. blood				
	Before	18	20	24	40
		20	20	40	44
		40	40	48	40
	5 hours after	S	40	S	S
		S	S	S	S
		S	S	S	S
	Control dosage Survival	0.001	0.0001	0.00001	0.000001
		40	20	40	40

REMARKS. Patient had pneumococcus Type III in sputum, with sterile blood culture. She received 1000 cc. blood of Donor 5 in three doses in 24 hours. Treated in oxygen tent, 50 per cent oxygen, for 5 days. Recovered.

**Case Histories.** CASE 1.—(Table 2.) Female, aged 58 years. The patient took sick with a chill, fever, malaise and cough 3 days before observation. Cough became productive 2 days later of blood-tinged sputum. On the third day of illness she was only moderately dyspneic, without cyanosis, and appeared comfortable. Lung signs revealed consolidation of the right lower lobe. Temperature was 103.6° F.; pulse, 106; respirations, 24. The sputum contained pneumococcus Type III. The blood culture was sterile. On the fifth day of illness the temperature was 103.2° F.; pulse, 112; respirations, 32. Consolidation had spread to the

left lower lobe. She was now more dyspneic, cyanotic and prostrated. Oxygen therapy was instituted with an oxygen tent, and the patient was kept in 50 per cent oxygen for the following 5 days, with clearing of cyanosis and considerable relief of dyspnea. However, the patient continued to appear toxic and the temperature persisted. On the seventh day of disease two direct transfusions of 300 cc. each from Donor 5 were given. No change in the clinical condition of the patient occurred, and on the following day another transfusion of 400 cc. of blood was performed. On the following day (8 hours later) the temperature dropped once to 97.8° F., but then returned to its previous level, without any fall in pulse or respiration or improvement in toxemia or prostration. The patient continued to run fever and an elevated pulse and respiratory rate for 8 days thereafter, when the temperature became normal and the patient gradually convalesced.

The patient's blood before injection contained no protective substance against pneumococcus Type III, but 5 hours after the second transfusion her blood protected against 0.01 cc. of culture with a virulence of 10-6 or 10,000 M.L.D. Notwithstanding the fact that protective substances in considerable degree were introduced into her blood and were present 5 hours later, the patient continued to have a long-drawn-out pneumonia, with an elevated temperature which did not subside until 8 days later. Just how long protective substance was present in her blood is impossible to say as no further tests were made. The course of the disease indicates that they were soon used up and that convalescence was not established until her own immunity mechanism became active. The fact that the patient recovered does not appear, therefore, to have been dependent upon the transfusion of immune blood.

CASE 2.—Male, aged 22 years. Following a cold, the patient became acutely ill 3 days before admission with cough, vomiting and pain in right chest. On examination he was acutely ill, with slight dyspnea. Lungs showed consolidation of the right lower lobe and right middle lobe. Sputum contained pneumococcus Type III, with blood culture sterile.

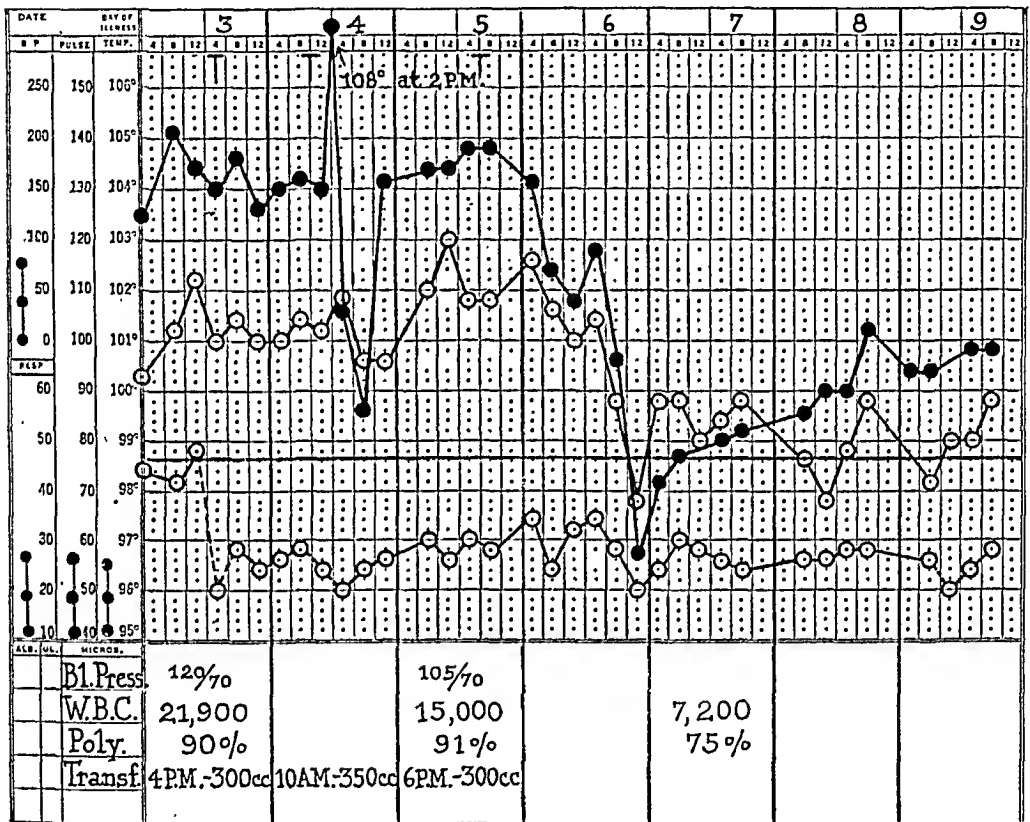
He was given an indirect transfusion of 300 cc. from Donor 5 on the third day of disease, without any reaction. On the next day an indirect transfusion of 350 cc. of blood was given which was followed by a severe chill, a rise in temperature to 108° F., a fall to 99.6° F. and a return to the previous temperature range of 104° F. No change in the clinical condition of the patient was apparent. On the following day, the fifth day of disease, the signs in the right lower lobe disappeared and consolidation of the right upper lobe appeared. A direct transfusion of 300 cc. of blood was then given without reaction, but without noticeable alteration in prostration or toxic appearance of the patient. The pulse rate assumed a higher level. The next day, the sixth day of disease, the temperature dropped to normal by crisis, with a corresponding fall in pulse and respiration and disappearance of prostration.

It was evident that no effect from any of the three transfusions was produced on the temperature, pulse and respiration (Chart I), or on the clinical appearance of the patient. The patient's serum contained protective substance after transfusion from the second to the sixth day of disease, although crisis did not occur until the sixth day. It is of interest that the course of the disease seemed uninfluenced by the presence of considerable amounts of Type III protective substance furnished by transfusion of immune blood.

CASE 3.—Male, aged 19 years. Twelve hours before admission the patient became sick with epigastric pain, vomiting and malaise. On examination he was acutely ill, flushed, prostrated and lethargic. Lung signs indicated beginning consolidation in the left upper lobe. Sputum contained pneumococcus Type II. Blood culture on admission was sterile.

On the following day consolidation spread to the left lower lobe and blood culture was positive for pneumococcus Type II. A direct transfusion of 600 cc. of blood from Donor 1 was given, following a preliminary phlebotomy of 600 cc. The next morning a phlebotomy of 500 cc. was performed followed by a direct transfusion of 600 cc. of blood from the same donor. No change in the clinical condition of the patient was observed. Two days later a spread to the right lower lobe occurred and the patient became cyanotic and much more prostrated. Oxygen chamber therapy was instituted with 45 per cent oxygen. The blood culture continued positive 6 hours after the second transfusion and 1 day after the last transfusion, but was

CHART I.



sterile 2 days after the last transfusion. The fever persisted and did not reach normal until 7 days after the last transfusion, when the patient was definitely better, and oxygen therapy was stopped. (Chart II.)

As seen in Table 3, no protective substance was present in the patient's serum on the first and second days after transfusions totaling 1100 cc. of the donor's blood which contained considerable amounts of Type II protective substance. (Table 1.) On the fifth day, and on the seventh day after transfusion, when recovery was established, protective substance appeared in the patient's serum in large amounts, obviously related to the natural course of the disease. Immune transfusion appeared of no benefit for the following reasons: (1) The absence of protective substance in the patient's serum and the presence of a positive blood culture after transfusion of immune blood; (2) a spread of consolidation to the right lower lobe after both transfusions had been given; (3) persistence of fever and prostration for one week after transfusions.



TABLE 3.—PASSIVE IMMUNITY IN PATIENT'S SERUM BEFORE AND AFTER IMMUNE TRANSFUSION.

Case No., age and sex.	Day after transfusion.	Survival after injection of PN <sub>2</sub> broth culture plus 0.2 cc. patient's serum.			
		0.01	0.001	0.0001	0.00001
3 Age, 19 Male	Before	20	20	20	20
			20	20	20
			20	40	20
	First	20	20	20	20
		20	20	20	40
		20	40	20	40
	Second	20	20	20	20
		20	20	20	20
		20	20	20	40
	Fifth	20	40	S	S
		20	50	S	S
		20	S	S	S
	Seventh	20	S	40	20
		40	S	40	60
		S	S	S	S
Controls:		0.01	20 hrs.		
		0.001	20 "		
		0.0001	20 "		
		0.00001	40 "		
		0.000001	40 "		
		0.0000001	40 "		
		0.00000001	40 "		
		0.000000001	20 "		

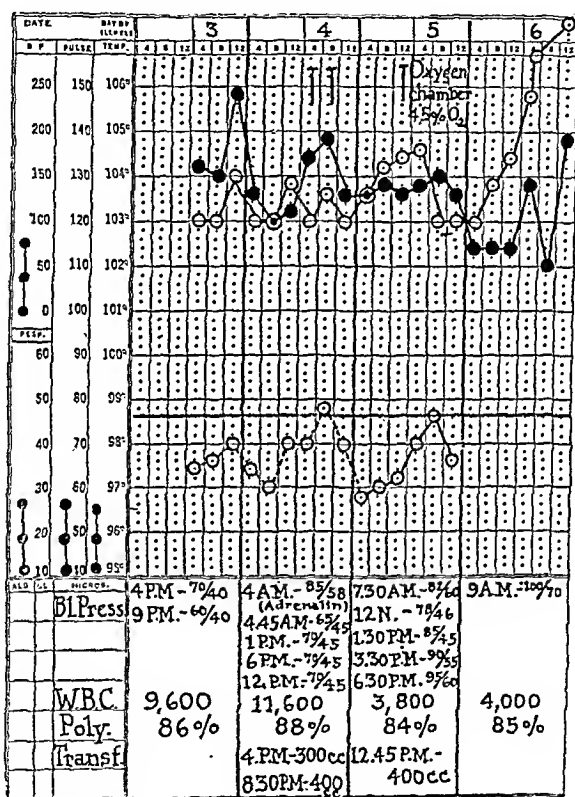
REMARKS. Patient had pneumococcus Type II in sputum with pneumococcus Type II bacteremia. He received 1100 cc. of blood of Donor 1 (see Table 1) in two doses in 16 hours. Blood culture persisted positive until two days after second transfusion. Treated in oxygen chamber, 45 per cent oxygen. Recovered.

CASE 4.—Male, aged 20 years. Twelve hours before admission the patient became ill with headache and pain in the left chest. On examination he appeared acutely ill and prostrated. Blood pressure was 70 systolic and 40 diastolic. Lung signs indicated beginning involvement of the left lower lobe. Two infusions of 500 cc. of 10 per cent glucose and stimulation by caffein sodium benzoate and adrenalin chlorid were given, with only temporary elevation of blood pressure to 85 systolic and 60 diastolic. Sputum contained pneumococcus Type II. Blood culture on day of admission was sterile, but on following day, the second day of disease, was positive for pneumococcus Type II. A direct transfusion of 300 cc. of blood from Donor 1 was given, followed in 4 hours by a transfusion of 400 cc. of blood from Donor 3 and 14 hours later by another transfusion of 400 cc. of blood from Donor 1. No improvement appeared to result from any of the transfusions. Blood pressure remained at 78 systolic and 46 diastolic. Blood culture persisted positive after each transfusion. Four hours after the last transfusion the blood count dropped from 11,600, polymorphonuclears 88 per cent to 3800, polymorphonuclears 84 per cent.



Signs of consolidation appeared in the right lower lobe, and cyanosis became marked. He was transferred to the oxygen chamber, oxygen concentration 45 per cent. Cyanosis began to diminish immediately, and the patient became much more comfortable. One hour after the patient was removed to the oxygen chamber blood pressure increased to 85 systolic and 45 diastolic, 3 hours later to 90 systolic and 55 diastolic and 5 hours later to 95 systolic and 60 diastolic. Quality of pulse was perceptibly fuller and firmer. On the following day the patient's condition was worse, a definite pericardial friction rub developed and that night he died. (See Chart III for clinical record.)

CHART III.



As seen in Table 4, no protective substance was present in the patient's serum after the first or third transfusion, even though the donors (Nos. 1 and 3) had developed considerable immunity against Type II pneumococcus.

The patient was seen in the first day of disease and treated on the second day with three transfusions of immune blood. No clinical improvement resulted, however, either in the signs of vasomotor shock, the disappearance of the positive blood culture or in the prevention of spread of the pulmonary lesion. The absence of any carry-over of protective substance from the donor suggested that the overwhelming toxemia quickly exhausted all the protective substance injected. The inhalation of 45 per cent oxygen was temporarily beneficial in increasing his comfort, as well as in terminating the signs of vasomotor shock, i. e., raising the blood pressure and increasing the volume and tension of his pulse.

TABLE 4.—APPEARANCE OF PROTECTIVE SUBSTANCE IN PATIENT'S SERUM BEFORE AND AFTER IMMUNE TRANSFUSION.

Case No., age and sex.	Day after transfusion.	Survival after injection PN <sub>1</sub> culture plus 0.2 cc. patient's serum.			Survival after injection PN <sub>2</sub> culture plus 0.2 cc. patient's serum.			Survival after injection PN <sub>3</sub> culture plus 0.2 cc. patient's serum.		
		0.001	0.0001	0.00001	0.001	0.0001	0.00001	0.001	0.0001	0.00001
4 20 years Male	Before	30	30	30	35	35	35	35	40	40
		30	30	30	35	35	35	35	40	40
		30	30	30	35	35	35	40		
	5 hours after first transfusion	30	30	30	35	35	35	40	40	40
		30	30	30	35	35	35	40	40	40
		30	30	30	35	35	35	40	40	40
	12 hours after third transfusion	30	30	30	30	30	30	30	30	30
		30	30	30	30	30	30	30	30	30
		30	30	30	30	30	30	30	30	30
	Controls:	0.000001	30 hrs.		0.000001	30 hrs.		0.000001	40 hrs.	
		0.0000001	30 "		0.0000001	30 "		0.0000001	40 "	
		0.00000001	30 "		0.00000001	30 "		0.00000001	40 "	
		0.000000001	30 "		0.000000001	30 "		0.000000001	40 "	

REMARKS. Patient had pneumococcus Type II in sputum and blood culture. He received 1100 cc. of blood mostly of Donor 1 (see Table 1) in 24 hours. Blood culture persisted positive after each transfusion. Treated in oxygen chamber, 45 per cent oxygen. Died.

CASE 5.—Male, aged 35 years. The patient was seized with a chill, followed by fever, cough and bloody sputum 6 days before observation. He became steadily worse, and on the sixth day was prostrated and toxic, markedly dyspneic and cyanotic. Lungs showed consolidation of the right middle and lower lobes and the left lower lobe. Sputum contained pneumococcus Type III. Blood culture was positive for pneumococcus Type III. Temperature was 105° F.; pulse, 140; respirations, 50.

He was put in an oxygen tent with 50 per cent oxygen, with diminution in cyanosis and a decrease in pulse rate. Three transfusions of 400 cc. each were given in 24 hours from Donor 4. No improvement in his clinical condition was observed and 12 hours later the patient died.

The blood culture before and after the first two transfusions was positive, but 2 hours after the last transfusion was sterile. However, no protective substance was present either before the transfusions or after 1200 cc. of immune blood were given.

The patient seemed fatally ill when first seen. The treatment by transfusion of immune blood did not appear to change the clinical condition of the patient in any way. His blood retained none of the protective substance introduced when tested two hours after the last transfusion.

CASE 6.—Male, aged 36 years. The patient became sick 4 days before observation, with chill, fever, cough and bloody sputum. On examination on the fourth day he was markedly prostrated, toxic, dyspneic and cyanotic. Lungs showed consolidation of the right lower lobe and the left lower lobe. The sputum contained pneumococcus Type III. Blood culture was positive for pneumococcus Type III. The patient was placed in an oxygen tent with 50 per cent oxygen, and three transfusions totaling 1200 cc. of blood were given in 24 hours from Donor 4. No change in the clinical condition of the patient took place, and on the following day he died.

Blood culture persisted positive after all transfusions. No protective substance was present for pneumococcus Type III before or 3 hours after the third transfusion. The injection of immune blood did not alter in any way the progressively fatal character of the infection.

CASE 7.—Female, aged 40 years. The patient took sick, with chill, fever, cough and bloody sputum 48 hours before observation. On examination she was prostrated, toxic, dyspneic and cyanotic. The lungs showed consolidation of the right lower lobe and beginning involvement of the left lower lobe. The sputum and blood culture both contained pneumococcus Type III. The patient was treated in an oxygen tent with 50 per cent oxygen, with considerable relief temporarily, decreased cyanosis, lower pulse and increased comfort in breathing. She was given 1000 cc. of blood in two doses from Donor 5 and 600 cc. of blood from Donor 4. However, her condition was unchanged on the following day in respect to temperature, prostration and toxic appearance of the patient, and on the second day after the last transfusion the patient died.

The blood culture remained persistently positive, and six hours after the last transfusion the patient's serum contained no protective substance against pneumococcus Type III. Although the patient was treated early in the disease, no effect was produced by relatively large transfusions of immune blood.

CASE 8.—Male, aged 61 years. The patient became ill 36 hours before admission, with chill and pain in the right chest. Examination revealed an elderly man acutely ill. The lung signs indicated consolidation in the left lower lobe, with scattered crepitant râles in the right lower lobe. The sputum contained pneumococcus Type III. Blood culture was sterile on the day of admission, positive for pneumococcus Type III on following day. Despite the use of digitalis, auricular fibrillation began the day after admis-

sion. A phlebotomy of 500 cc. of blood was performed on the day after admission followed by a direct transfusion of 600 cc. of blood from Donor 4. Eight hours later a second direct transfusion was given from Donor 2. No clinical improvement resulted, the patient became steadily weaker and died the next day.

No protective substance was present in the patient's serum on the day following the two transfusions totaling 1200 cc. of blood. Blood culture persisted positive. The patient was a poor subject, but no betterment resulted from the transfusions of immune blood.

**Discussion.** Of 8 patients who were treated by immune transfusion, 6 were due to pneumococcus Type III and 2 to pneumococcus Type II. Four of the 6 Type III cases had a bacteriemia and all died. The 2 Type III cases with sterile blood culture survived. Of the 2 cases of Type II pneumonia with positive blood culture, 1 died and 1 survived.

The immediate effect of the transfusion on the clinical condition of the patient was negligible. No lessening of toxemia, prostration, cyanosis or dyspnea was observed. In four fatal cases, the blood culture was not rendered sterile, nor was the spread of pulmonary consolidation checked. The determination of protective substance in the patient's blood before and after transfusion of immune blood showed an absence of the introduced protective substance in all the 5 fatal cases. Of the 3 who survived, 1 showed no protective substance in his serum until 2 days following the last transfusion, which therefore could not be ascribed to the introduction of immune blood. In 2 cases of pneumococcus Type III infection with sterile blood culture, the patient's serum contained protective substance after immune transfusion although not before. Their clinical course, however, was so long drawn out that it would not be possible to ascribe recovery to the protective substances introduced by transfusions.

**Conclusions.** 1. Eight patients with pneumococcus lobar pneumonia, 6 due to Type III and 2 due to pneumococcus Type II, were treated by transfusion of 1000 to 1600 cc. of blood from donors immunized over long periods of time.

2. No favorable effect was observed on the clinical condition of the patient as a result of any of the transfusions. The introduction of protective substance present in the donor's blood could not be demonstrated in the patient's blood in the 5 fatal cases and appeared to have no influence on the course of the disease in the 3 recovered patients.

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THE CHOLAGOGUE EFFECT OF THE INTRAVENOUS INJECTION  
OF SODIUM DEHYDROCHOLATE, WITH A RÉSUMÉ  
OF LITERATURE ON BILE SALT METABOLISM.\*

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BEFORE we report the results of our study as to the cholagogue effect of sodium dehydrocholate, we feel it important that a review of the literature bearing on the physiology of bile salt metabolism and its influence on bile output should be discussed for the following reason: Any study such as the one here reported is of limited value unless all of the factors as hereafter discussed are taken into consideration and suitably controlled. We acknowledge that, save for adopting a standard preliminary diet for one meal before testing the cholagogue effect of sodium dehydrocholate, we have not adhered to the criteria which we now believe important and which should be utilized in further cholagogue and choleretic clinical studies.

**Bile Salt Metabolism.** Bile has as its more important and recognized constituents bile salts, bile pigments, cholesterol, certain inorganic salts and water.

Bile salt metabolism and the hepatic biliary secretory mechanism is fundamentally involved in the discussion of any phase of the cholagogue activity or the choleretic action of any drug or group of drugs.

Cholagogue action has to do with volume of bile output without regard for the quantitative amounts of the various constituents, while choleretic action has to do with the quantitative amounts of the individual biliary constituents other than water. The importance of distinguishing between these two types of hepatic activity becomes obvious when considering bile secretion and the factors governing it.

The anabolic phase or constructive portion of this complex metabolism is today an unknown process. It necessarily involves the origin and formation of the precursor substances and their collection and transmission to the hepatic epithelial cell, which is believed to be the seat of bile salt synthesis. Regarding the precursor substances themselves nothing is known. The catabolic or destructive phase involving the destruction of excess bile salts also remains obscure.

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As in other complex metabolic systems in the human body, may we not suppose that a regulatory mechanism governs the anabolic and catabolic phases of bile salt metabolism (and subsequent bile secretion), because we are cognizant of the fact that the bilesalts in themselves are the chief and practically the sole bile secretory stimulants.<sup>2</sup> Such a regulatory mechanism has been suggested by the investigators in the field of bile salt metabolism.

Regarding the elimination of bile salts, the only outlet recognized at the present time is the bile itself. Throughout this paper the terms bile salts and bile acids are used interchangeably.

Bile salt metabolism and concomitantly bile salt and bile production are theoretically influenced by three major factors: (1) Exogenous, embracing principally foods and drugs; (2) endogenous, embracing principally the effects of endocrine glandular secretions and endogenous nitrogen or protein metabolism; (3) the entero-hepatic factor. A consideration of these factors and their relation will be attempted, especially as brought out by the work of Whipple and his colleagues, which is outstanding in this field.

Whipple and Smith,<sup>1</sup> working with dogs in a study of bile salt metabolism, found that on a given diet of salmon and bread there is a definite level of bile salt output per kilo of body weight during 24 hours. If to these bile-fistula dogs their entire 24-hour output of whole bile is added to the salmon-bread diet a rise in the bile salt output occurs at a higher plateau-like level. Whereupon, if additional or supplementary bile feeding is now added there occurs a further rise to a higher level of output; if this supplementary feeding is withdrawn there is a prompt fall back to the previous plateau-like level. Furthermore, when very large doses of bile salts alone are given only a part is eliminated in the bile and the fate of the bile salt is unknown. Due consideration is taken of the possibility that small amounts of bile salt escape in the urine and that, although the feces become dark in color with some diarrhea with heavy bile salt feeding, accurate quantitative determination of bile salts in the feces has not thus far been found possible. Thus it appears that the body can eliminate in the bile only a certain amount of the bile salt and the disposition of the excess is unknown. It is further shown that within certain limits quantitative absorption of bile salts from the intestine and resecretion by the liver is true, and this fact plus a constant endogenous as well as exogenous production day by day would soon lead to an absurd excess body content or, as Whipple aptly puts it, "the dog would soon become a pillar of bile salts."

Obviously there must be some sort of a regulatory mechanism by which a balance is maintained in this much overlooked phase of body physiology. Smith, Groth and Whipple<sup>2</sup> observed that the bile salt secretion in dogs in spite of a single daily feeding was quite uniform during the 24 hours. Considering the three 8-hour

periods, beginning at 8 A.M., the bile salt output was practically the same except for the night period embracing the time of bodily rest, when it was slightly lower than for the evening period, representing the period of maximal digestive activity. Therefore, this so-called base line level of bile salt output is rather uniform for a given dog on a salmon-bread diet. In addition, the institution of sugar feeding or fasting following the salmon-bread diet resulted in a gradual fall in bile salt output during the following 2 or 3 days; resumption of the salmon-bread diet then called forth a rise in output over a period of 2 or 3 days to the previous salmon-bread level. This gradual rather than abrupt fall and rise respectively following changes in the diet suggests a storage of the precursor substances incident to bile salt synthesis to be gradually utilized as fasting continues, and when a favorable diet is resumed suggests a storage of the precursor material to be utilized when an emergency need arises. Wisner and Whipple<sup>3</sup> again corroborated the above findings. They determined the bile salt output during four 6-hour periods, and results showed a remarkably uniform level for each period. Greene, Rowntree, *et al.*<sup>4</sup> observed bile acid secretion in the bile of bile-fistula dogs for 30-minute periods following the oral administration of bile acids and found little change during the first 30-minute period, but thereafter a striking increase in the bile acid output occurred during the second, third, fourth and fifth 30-minute periods, corresponding in part to the volume of bile.

**The Rôle of Hepatic Epithelium.** The hepatic epithelial cell probably plays an important rôle in the secretion of bile salts and of bile itself. To it has also been ascribed the function of synthesis of the bile salt molecules, although definite proof is lacking. Concerning the hepatic epithelium with its highly complex physiology little is known. Its internal or intracellular metabolism and its relation to bile salt synthesis and secretion are obscure. However, in the final analysis, and in the face of our ignorance of the origin and formation of the precursor substances of bile salt construction, and in spite of our lack of knowledge concerning the seat of bile salt synthesis and bile salt destruction, we should assign to the hepatic epithelial cell an important rôle in bile secretion and bile salt metabolism upon the few facts elicited by the investigations in this particular field.

Cramer and Ludford<sup>5</sup> conclude from their study on the cellular mechanism of bile secretion and its relation to the Golgi apparatus of the liver cell, in which they utilized the livers of mice, rats and guinea pigs both normal and pregnant, that the bile constituents appear in the Golgi apparatus of the liver cell which in the process of bile secretion first enlarges and then fragments. The fragments are dispersed throughout the cytoplasm and upon reaching the periphery pass their contents into the intercellular bile capillaries.

The possibility that the intrahepatic portion of the enterohepatic

circulation of bile salts exerts an influence on the internal metabolism of the hepatic epithelial cell, which is essentially concerned in many vital processes, has been suggested.<sup>1</sup>

A stimulatory action on the liver cell has been ascribed to tryptophane,<sup>6</sup> isatin and even indigo, in view of the marked cholagogue effects of these substances, despite sugar feeding which in itself brings about marked diminution of volume and extreme concentration of the bile. A relationship between bile salts and the above stimulative substances is suggested because of their similar effects on the hepatic epithelium.

Chloroform and phosphorus have long been recognized as liver poisons. Smyth and Whipple<sup>7</sup> administered small doses of chloroform by inhalation and by stomach tube to dogs and found a marked reduction in bile salt output, to 10 per cent of normal or even less. Associated with these small doses of chloroform there was a functional depression of the liver cell, but no actual liver cell injury or organic change could be demonstrated. Phosphorus, even in lethal doses, does not seem to produce the marked diminution in bile salt output that is caused by small doses of chloroform, even though organic injury to the liver cells may be present in the phosphorus poisoning.

The metabolic activity of the hepatic epithelium has been found by Greene and Rowntree<sup>4</sup> to be disturbed in dogs following operative removal of the gall bladder, under amytal narcosis, with cannulization of the common duct, with coincident depression of the bile salt secretion. The liver bile collected for a period of 6 hours after introduction of bile salts into the duodenum of the animal, following such an operative procedure, showed a lessened bile salt output. This apparent disturbance of hepatic intracellular metabolic activity and depressant effect upon bile salt secretion was probably due either to the operative procedure itself, to the anesthetic used, or to disturbances in the portal circulation. The functionally deficient liver,<sup>8</sup> such as one with an Eck fistula, secretes less than half the normal amount of bile salts on a standard diet during a definite period. This, therefore, offers an additional link in the chain of evidence pointing toward the liver cell as the center of bile salt synthesis.<sup>9</sup>

Bile secreted against an abnormally high pressure, such as that existing in partial obstruction of the common bile duct, contains less amounts of the biliary constituents, such as bile salts, bile pigment and cholesterol. The probable mode of action seems to be a depression of the functional activity of the liver cells.

The protective influence on hepatic epithelium,<sup>10</sup> exerted by certain dietary factors, such as sugar and those diets which are rich in carbohydrates, and the parenchymatous organic foods, such as liver and kidney, against damage by chloroform poisoning seems to have been established. The feeding of these specific dietary



substances to dogs prior to chloroform administration seems to protect the liver cell from injury, probably by virtue of some adjustment or change in the cellular metabolism itself, rather than because of substances circulating in the blood stream.<sup>11</sup>

Proteose intoxication is associated with a characteristic symptomatology, together with a profound disturbance in the endogenous nitrogen metabolism yielding increased nitrogen and increased blood nonprotein nitrogen, indicative of considerable body protein catabolism. Bile salt production is reduced as a result of proteose intoxication, probably as a result of hepatic epithelial cell injury, functional in type, since there is no evidence of histologic change. This offers a further confirmatory fact in the localization of bile salt synthesis in the liver cell.

**Exogenous Factors.** The exogenous factors which influence bile salt metabolism and subsequently bile salt production and bile secretion are principally dietary. In the dog it has been demonstrated<sup>8,12,13</sup> that food protein is of foremost importance in the determination of the level of bile salt output. Meat and meat products cause a pronounced increase in the bile salt output. Alcoholic extractives of meat have no effect on bile salt output, although the residue loses none of its power of increasing production. Commercial beef extracts may contain some elements causing increase in bile salt production. Yeast nucleic acid is not effective in changing bile salt output. Lipoids and cholesterol when fed to dogs yield no change in bile salt secretion.

The various dietary factors may influence principally the volume of bile or the content of any of the bile constituents. In our present discussion, however, we are concerned with the volume of cholagogue effects, and the bile salt secreted is considered the most potent cholagogue factor known.

Okada,<sup>14</sup> working with bile-fistula dogs found that raw egg white, boiled egg white, fat, oil, soap solution, acids, Witte's peptone, meat extractives and bile salts or bile itself introduced into the stomach caused an increase secretion of bile. Whereas he found that pure cane sugar, cakes baked of starch and sugar, and water had no effect on the bile secretion when introduced into the stomach. Whipple, Smith and Smyth<sup>6,13</sup> found that tryptophane occupies a unique place among those substances influencing the secretion of bile. Gelatin feedings in bile-fistula dogs results in bile salt production at a lower level than that of salmon-bread diet. This observation suggests the possibility that one of the amino acids not present in gelatin plays an important rôle in bile salt production and bile secretion. Gelatin plus tyrosin yields no effect. Gelatin plus tryptophane immediately raises bile salt output to slightly below the maximal values obtained on a meat diet. This observation would lead one to ascribe the determining rôle to tryptophane, but on a tryptophane plus sugar diet no increase in

bile salt output occurs. The conclusion may be that there is some other substance in gelatin plus tryptophane necessary to raise bile salt output. This cholagogue result of gelatin feeding shows a definite fall from day to day, more so than the fall in bile salt output on gelatin plus tyrosin and gelatin plus hydroxyphenylglycin diets. Cholagogue action is markedly increased on a gelatin plus tryptophane diet, slightly more on a tryptophane plus salmon-bread diet with coincident rise in bile salt output. Resumption of fasting and sugar feeding reduces bile salt output to near the fasting base line level. Tryptophane given now with sugar feeding results in a fall to the base line level. This suggests that tryptophane alone is inefficient in influencing bile salt secretion. Resumption of a salmon-bread diet now results in a rapid and unusually high output of bile salts, which suggests some influence of the preceding tryptophane feeding. Tryptophane plus sugar feeding yields a notable cholagogue result but no increase in bile salt output, which is in marked contrast to sugar feeding alone which produces extreme bile concentration. Tryptophane, isatin and even indigo added to the diet of dogs cause a conspicuous cholagogue effect, suggesting an influence on the hepatic epithelium separate and distinct from the bile salts as factors in bile secretion, or these various factors may be interrelated.

Bile salts themselves definitely influence bile salt secretion and bile secretion. Wisner and Whipple<sup>3</sup> found that the oral administration of taurocholic acid in bile-fistula dogs results in a marked rise in bile salt output during the first 6-hour period and a return to a normal level in the second 6-hour period. However, the cholagogue effect is still marked during the second period, indicating dissociation of bile volume from bile salt output. The appearance of bile acids in the bile is delayed and their secretion prolonged when administered by mouth,<sup>4,15</sup> in contrast to the prompt appearance and secretion when administered intravenously. Approximately the total quantity of bile acids injected intravenously was recovered in the bile within 2 hours after administration. Bile acids are eliminated rapidly<sup>15,16</sup> after administration with even maximum dosages compatible with recovery of the animal and their concentration in the blood stream persists for only 1 or 2 hours.<sup>16</sup> Bile or bile acids by oral administration result in an increase in the bile acids in the portal vein while the amount in the systemic circulation is unchanged.<sup>17</sup> Injection of bile into the duodenum results in an increased pancreatic secretion as well as increased flow of bile. Similar introduction of bile into the ileum causes increased flow of bile with no effect on pancreatic secretion, as follows the intravenous administration of bile salts. Although the intravenous injection of purified secretin causes a marked flow of pancreatic juice and augments the flow of bile, it is believed that this effect is secondary and is dependent upon its prior action on

the pancreas with the products of pancreatic metabolic activity then passing into the portal blood and thereby stimulating bile secretion in the liver.

The enterohepatic circulation of the bile salts notably influences the secretion by the liver, quantitative absorption from the intestine and resecretion by the liver. It is an omnipresent factor to be considered in the metabolism of bile salts and also in secretion of bile volume as well as quantitative bile salt elimination. A regulatory process is undoubtedly present to maintain a balance between anabolic and catabolic phases of bile salt metabolism.<sup>18</sup> Unfortunately mystery still enshrouds this important stabilizing mechanism.

Drugs have long been supposed to possess cholagogue powers. Smyth and Whipple<sup>19</sup> found that calomel, hydrochloric acid, sodium salicylate and ethyl alcohol show no constant effect on bile secretion or bile salt output. Atropin and pilocarpin likewise cause no observable change in the bile secretion. Phlorizin and quinin are similarly powerless in this respect. Hemoglobin<sup>18</sup> injected intravenously produces no change in bile salt output. The salicylates<sup>18</sup> have never produced constant change in bile salt output. Okada,<sup>14</sup> working with bile-fistula dogs, found that the following drugs increase the flow of bile, namely, sodium salicylate, salol, chloral hydrate, cream of tartar and alcohol. Atropin produces a slightly lessened flow and pilocarpin a slightly increased flow of bile. Nicotin results in an inconstant increase in bile secretion. Calomel is without effect on bile flow.

Vigorous exercise<sup>20</sup> exerts no effect on the bile flow. Hot weather depresses markedly the flow of bile in dogs, although the animals remain in good general condition. Intercurrent diseases unassociated with jaundice exert a marked depressant effect on bile secretion, in fact the flow may almost cease. It is quite interesting to note that in the presence of these conditions the bile secretion is unaffected by the oral administration of the best cholagogue, namely, bile itself. This suggests that bile or bile salts act most favorably when the dog is healthy, the weather not too oppressive and the food intake sufficiently abundant and proper. Operative procedures<sup>18,20</sup> on the gall tract result in a scanty bile secretion for the first few days postoperatively, and not until 7 to 10 days after operation does the bile resume its usual appearance. In dogs under amytal narcosis and operative gall tract procedures<sup>4</sup> there was a notable diminution in bile output by the liver following the operation. In the presence of an abnormally high pressure,<sup>9</sup> such as occurs in partial obstruction of the common bile duct, there results a greater decrease in the amounts of total bile constituents than in the volume of bile secretion.

**Endogenous Factors.** The endogenous factors which influence bile salt metabolism are apparently closely associated with body protein metabolism. The base line level of bile salt output in the

fasting dog is a fairly constant one and remains unchanged during long periods of fasting.<sup>2</sup> This suggests that bile salt secretion represents the endogenous portion of bile salt metabolism and is probably the result of body protein breakdown. Whipple's work<sup>18</sup> suggests very definite relationship between body protein metabolism and bile salt metabolism. An interesting parallelism<sup>12</sup> exists between bile salt output and urinary nitrogen, namely, in fasting and sugar feeding there is low bile salt output and low urinary nitrogen, while in high meat diets a high bile salt output occurs, with a high urinary nitrogen. This suggests that body protein or food protein is the source of an essential precursor substance in bile salt synthesis.

The influence of the secretions of the endocrine glands on bile and bile salt secretion is noteworthy. Downs and Eddy<sup>21</sup> found that secretin increases the amount of bile secreted. Adrenalin depresses the amount of bile as do mammary, orchic, ovarian, pancreatic and thymic gland substances. Spleen and thyroid gland substances do not affect the amount of bile secreted in a constant or definite manner in cats. The effects of thyroid substance and thyroxin<sup>11</sup> on bile secretion or bile salt production in dogs are negative. Mellanby<sup>17</sup> believes that secretin is not primarily a cholagogue, but increases the flow of bile by virtue of its stimulus to pancreatic activity. The resultant metabolic products are passed into the portal blood stream and thence to the liver, where they excite hepatic activity which results in an increased secretion of bile. Downs<sup>22</sup> and also Okada<sup>14</sup> corroborated the views of Downs and Eddy<sup>21</sup> and of Mellanby<sup>17</sup> as regards the influence of certain endocrines on bile secretion.

**Enterohepatic Factors.** The enterohepatic factor concerns the secretion of bile salts by the liver cells, their discharge into the duodenum in the bile flow, their reabsorption by the intestinal mucosa into the portal circulation and their subsequent resecretion by the liver cells. This is the so-called enterohepatic circulation of bile salts and is, therefore, definitely related quantitatively to the exogenous and endogenous factors as previously discussed.

In addition some discussion should be given to bile salt synthesis or the anabolic phase of bile salt metabolism. What follows represents the comparatively little that is now known of this complex physiology.

**Bile Salt Synthesis.** Cholic acid<sup>23</sup> appears to be the limiting factor in bile salt metabolism. Taurin is thought to be available in excess in the body for union with any newly formed cholic acid radicals present, thus yielding taurocholic acid. Cystin seems to be the source of most of the taurin. It has been suggested by Foster, Hooper and Whipple<sup>23</sup> that the indol ring of indigo and isatin is probably utilized by the body to synthesize cholic acid. A strong physiologic action between taurin and cholic acid appears to exist in the body.

During full diet periods taurin seems to be more abundant in the body for linkage with cholic acid than during the fasting periods, or at least it is more available. Cholic acid seems to have no physiologic relationship to cholesterol and apparently cholesterol has no influence over cholic acid metabolism, because cholesterol when fed alone or combined with taurin has no influence on bile acid secretion.<sup>23</sup> Furthermore, terpene hydrate or camphor fed alone or in combination with taurin has no influence on bile acid production. Red blood cells fed alone or hemolyzed and injected intravenously have no effect on bile acid secretion.

Foster, Hooper and Whipple<sup>8</sup> further found that the bile acid output in a fistula dog following a long fasting period will not react to the usual high level on the resumption of a high-protein diet. This fact suggests the utilization of precursor substances of bile acid formation in some other body process, such as the supplying of some important substance relative to body protein which has been depleted during the fasting period. Whipple<sup>18</sup> again points out some very interesting facts concerning bile salt synthesis. He states that the taurin of taurocholic acid and the glycocholic acid are amino acids, both of which are present in the body. Glycocholic acid may be formed within the body and taurin is probably in large part from the cystin of the food or body protein. Taurin and glycocholic acid are probably present in excess in the body under modern conditions and are available for bile acid formation. Cholic acid is the key substance of bile acid synthesis and is, therefore, the limiting factor in its formation. The origin of cholic acid is unknown, nor is anything known of its catabolism or its elimination other than by way of the bile excretion. It is a complex substance containing no nitrogen, and has been assigned a relationship to turpentine and camphor. Taurin itself administered intravenously exerts no effect on bile acid secretion. Taurin and cholic acid by mouth have the same effect on bile acid secretion as taurocholic acid orally administered, both of which increase bile acid production. Taurin given intravenously and cholic acid given by mouth cause increased bile acid output. These facts suggest a very strong physiologic relationship between these substances in the body tissues.

An additional fact showing the importance of taurin in the synthesis of bile acids occurs when cholic acid is fed to dogs. During long fasting periods a minimal output of bile acids results; but if cholic acid is fed during full diet periods it yields a maximal output of bile acids. This observation is evidence of the available supply of taurin which was low during fasting and high during full diet periods.

Greene, Aldrich and Rowntree<sup>16</sup> suggest that a probable failure of bile acid synthesis occurs after the first few weeks of experimental jaundice produced by obstruction of the common bile duct, because they find that the bile acid content of the blood increased rapidly

immediately following the onset of obstruction, then decreased during the first few weeks of jaundice and finally tends to return to a normal level. In addition, they find the rate of elimination of bile acids administered intravenously to be greatly delayed in the presence of experimental jaundice.

Finally, as a preliminary to our study of an alleged nontoxic bile salt it is necessary to review some points in regard to the toxicity of bile salts and their therapeutic application.

**The Toxic Factor in Bile.** Bile has long been known to be markedly toxic to human tissues. The effects of bile peritonitis with its severe toxic manifestations and usually fatal result are well known among investigators and surgeons. The use of intravenous bile salts, such as sodium taurocholate and glycocholate, as well as whole bile solutions, is attended with marked toxic reactions even in relatively small doses.

The cholates,<sup>24</sup> and therefore inferentially the bile salts, occupy a far more important position in the normal, as well as diseased, economy than the other biliary constituents. Furthermore, the bile salts are undoubtedly the most injurious factors in biliary disturbances. The effect of diversion of bile<sup>25</sup> into the systemic and portal circulations, by anastomosis of the common bile duct and gall bladder with branches of the portal vein and vena cava, resulted in the death of the animals with such portal anastomosis in from 3 to 7 days and in animals with systemic venous anastomosis in from 18 to 48 hours.

Determination of the toxicity of purified bile preparations resulted in the conclusion by Still<sup>26</sup> that the cholate radical is responsible for the toxicity of bile. Further, as determined by intravenous administration in the dog, by intraperitoneal administration in the rabbit and by intralymphatic administration in the frog, the order of toxicity of the naturally occurring bile salts is: (1) Cholic acid; (2) desoxycholic acid; (3) glycocholic acid. Also, that bilirubin is a nontoxic substance and that the bile acids are the most toxic substances in the bile.

Horrall and Carlson found that the intravenous administration of whole gall bladder bile from one dog to another is dependent upon the amount of bile injected and the rate of injection.<sup>27</sup> Death of the dogs resulted from small amounts of the whole bile injected rapidly, while larger doses slowly administered produced only transient symptoms. However, in spite of the fact that early death does not result from such injections, the dogs appear to have a marked lowering of their resistance to infection, notably pneumonia. These authors suggest that the bile salts may cause dissolution of the limiting membrane of tissue cells, may change their surface tension and may destroy the normal cellular metabolism. Furthermore, bile injected in sufficient quantity to be fatal in 24 hours is not modified in its toxic effects by the presence of bacteria.

The toxicity of bile is unaffected by boiling or freezing. The dialyzable portion of whole bile possesses the same degree of toxicity as whole bile, while the nondialyzable portion possesses no element of toxicity. The cholate radical is the toxic portion of the bile salts, such as sodium taurocholate and sodium glycocholate; the absence of any toxic element in bilirubin is again corroborated.

The results of a study by Macht and Hyndman<sup>28</sup> of the relations between the chemical structure of bile acids and their reactions on plants and animals showed that the taurin radical of sodium taurocholate and the glycin radical of sodium glycocholate possess no toxicity toward plant and animal protoplasm; that cholic acid exerts a marked depressant effect on the neuromuscular and cerebrospinal reactions of rats operating in the circular maze; that the cholic acid exerts a marked depressing effect on the growth of seedlings; that the toxic manifestations of bile acids on animal as well as plant protoplasm are attributable to the cholic acid portion of the bile salt molecules. The effect of sodium taurocholate on the permeability factor of tissues has been shown by Osterhout<sup>29</sup> to decrease it, and it, therefore, suggests a possible antagonism to the effects of sodium chlorid and other substances, which thus increase the permeability factor in tissues.

**Nontoxic Bile Salts.** Thus it may be seen that the use of sodium taurocholate and sodium glycocholate orally and to a considerably greater extent intravenously was a highly perilous procedure in human beings because of their extremely toxic action. Nontoxic bile salts preparations have long been sought that they might be used as cholagogues and cholcretics in the treatment of hepatic and biliary tract disease.

Neubauer and Pohl,<sup>30</sup> working in different laboratories, both found that apocholic acid, desoxycholic acid, dehydrodesoxycholic acid and dehydrocholic acid were the only bile acids of the whole group under investigation which had a definite secretion-stimulating action. Rabbits were used as the experimental animals because of the extraordinary regularity of their bile secretion. Neubauer and Adlersburg<sup>30</sup> demonstrated that a greater flow of bile followed the administration of dehydrocholic acid than occurred following the giving of cholic acid. Furthermore, the toxicity of dehydrocholic acid has been shown to be minimal (1) by virtue of its extremely slight hemolytic effect; (2) because of its minimal toxic effect on the isolated heart of a frog, showing it to be one-twenty-fifth as toxic as desoxycholic acid; (3) by virtue of its increased tolerance in relatively large doses by the body as a whole. The maximum nonfatal dose is 100 times that of desoxycholic acid and 11 times that of sodium taurocholate.

Neubauer<sup>31</sup> also found that the administration of dehydrocholic acid to human beings by the intravenous method has demonstrated that there is a striking increase in the quantity of bile secreted;

that the specific weight and relative and absolute dry residue of the bile increased, and that the viscosity tends to increase. Furthermore, the use of the sodium salt of dehydrocholic acid as a cholagogue was confirmed by Wakefield, Powelson and McVicar,<sup>32</sup> who found that it definitely caused an increased flow of bile in 18 out of 20 human patients studied.

With this preliminary discussion of the literature, we now proceed to report the results of a clinical study of the cholagogue effect of the alleged nontoxic sodium salt of dehydrocholic acid.

**Clinical Study of Sodium Dehydrocholate.** Dehydrocholic acid was first introduced into therapeutics by Adlersberg and Neubauer in 1925. It occurs as a fine, crystalline, colorless powder, forming needle-shaped crystals and having a melting point of 233° C. The sodium salt of dehydrocholic acid, known as sodium dehydrocholate (trade name, Decholin-Sodium), is readily soluble in water, less readily in alcohol, producing a weakly alkaline solution having a bitter taste. Dehydrocholic acid is produced by oxidizing cholic acid.

**Purpose of Study.** Our present investigation was made to determine only the cholagogue or volume effect following the intravenous administration of sodium dehydrocholate. We realize the difficulties and probable criticism of the duodenal collection of biliary secretion and its source of error especially in quantitative volumetric determinations. We are cognizant of the fact that the external secretion of the pancreas is poured into this area; that the duodenal secretion is present; that gastric secretion is intermittently entering the duodenum. Therefore, accurate quantitative estimation of biliary secretion has been impossible. However, observations of the physical characteristics and color changes in the bile made during the study lead us to conclude that this error is reduced, if one is accustomed to watching the ordinary return of bile obtained by duodenal tube biliary drainage.

The present study is concerned then with the collection of duodenobiliary secretion by means of the duodenal tube in a series of patients chosen at random from those undergoing treatment in this department. The series comprises of 21 patients suffering from various types and degrees of gastrointestinal disturbances.

**Procedure.** A standard meal, consisting of one piece of buttered bread and one cup of tea, was given each patient 6 hours prior to intubation. Nothing by mouth was permitted thereafter. Duodenal intubation was accomplished and drainage was instituted until a constant flow of bile was obtained or the tip was definitely located in the duodenum by auscultation, whereupon 10 cc. of a 20 per cent solution of sodium dehydrocholate (Decholin-Sodium) were slowly administered intravenously. Thereafter for 90 minutes all fluid returning through the tube was collected in 9 test tubes—a tube for each 10 minutes of flow.



The control study was instituted on the same group of patients 1 week after the above procedure, utilizing the same meal with identical instructions and time limits. The duodenum was intubated, and after a constant flow of bile was obtained all the drainage was again collected for 10-minute periods, for a total of 90 minutes.

The following data concerning each of the 10-minute specimens collected were recorded: (1) Quantity of bile in cubic centimeters; (2) specific gravity; (3) color; (4) type of bile, whether A, B or C,\* with reference to its origin in the biliary tract; (5) in addition, blood pressure determinations were made 20 minutes before administration of the sodium dehydrocholate and at 30-minute intervals thereafter; (6) the radial pulse rate was noted at the same intervals as the blood pressure determinations were made; (7) untoward effects were recorded as immediate, *i. e.*, during the intravenous administration, delayed, occurring during the time of the test, or remote, occurring during the week following the actual study.

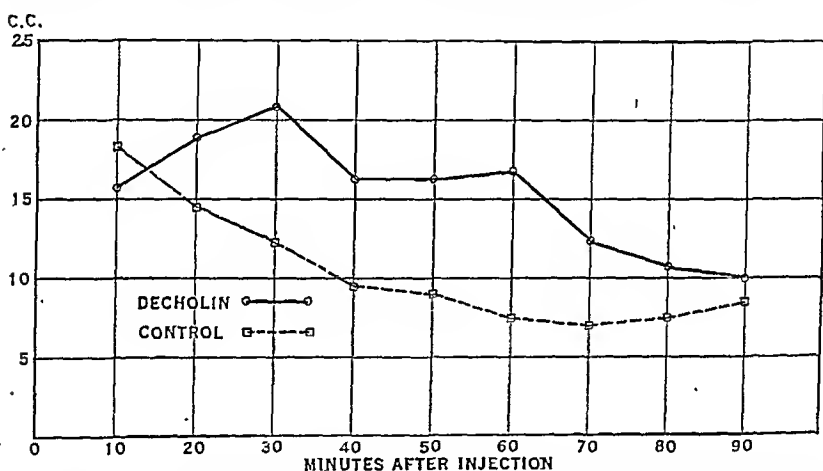


CHART I.—Composite graph of 21 patients showing the average amount of bile removed each 10 minutes over a period of 1½ hours, with and without decholin-sodium, administered intravenously.

**Analysis of Results. 1. Quantity of Bile.** (See Table 1 and Chart I.) The total quantity of return for the 21 patients over a 90-minute period after injecting Decholin was 2817 cc., or an average return of 134 cc. for each patient.

\* "A" bile is arbitrarily designated as that derived chiefly from the extrahepatic ducts after Oddi's sphincter has relaxed.

"B" bile is designated as that derived chiefly from the gall bladder. It is darker yellow-brown than either "A" or "C" bile, due to the concentrating ability of the gall bladder.

"C" bile is designated as that derived chiefly from the liver, as freshly secreted bile. This bile is usually a light lemon-yellow color, offering a definite contrast to the darker yellow-brown, green or black "B" bile.

For further information consult: *Non-surgical Drainage of the Gall Tract*, by B. B. Vincent Lyon, published by Lea & Febiger, Philadelphia, 1923.

In the control experiment the return measured 1883 cc., an average of 80+ cc., or an average increase of 54 cc. after intravenous injection of sodium dehydrocholate.

Four patients showed less output of bile on the day of intravenous injection than on the control day. The amounts of these 4 cases were: following injection, 325 cc.; control, 421 cc.

Inasmuch as these figures were included in the total returns for the whole 21 cases who were tested, it is necessary to deduct these amounts if we wish to reach a conclusion concerning the bile flow response in the patients who reacted favorably to the injection. Thus 17 patients returned 2492 cc. following injection and on control testing returned 1462 cc. Average increase in these 17 cases was 60+ cc. The greatest individual increase was 120 cc. The greatest individual decrease was 46 cc.

The rate of flow is indicated in Table 1. The cholagogue effect of sodium dehydrocholate was most brisk at 20 and 30 minutes after injection, slightly less for the next 30 minutes, then becoming less during the final half hour.

TABLE 1.—AVERAGE QUANTITY OF DUODENAL RETURN IN 21 CASES FOLLOWING INTRAVENOUS INJECTION OF SODIUM DEHYDROCHOLATE COMPARED TO CONTROL STUDY WITHOUT SODIUM DEHYDROCHOLATE AT 10-MINUTE INTERVALS FOR 90 MINUTES.

Minute intervals.	Cubic centimeters after injection.	Cubic centimeters from controls.
10 . . . . .	15.6	18.2
20 . . . . .	19.0	14.4
30 . . . . .	20.5	12.1
40 . . . . .	16.1	9.5
50 . . . . .	16.0	9.0
60 . . . . .	16.5	6.5
70 . . . . .	12.4	5.9
80 . . . . .	10.75	7.4
90 . . . . .	10.2	8.0

2. *Specific Gravity.* It was not possible to arrive at an accurate conclusion relative to change of specific gravity. This was because: (1) The individual returns were in some instances too little to permit of estimation by even the smallest hydrometer; (2) the presence of the tip alone in some of the control tests seemed after 10 to 60 minutes to bring about a partial gall bladder response resulting in a delivery of various amounts of concentrated B bile having a higher specific gravity than the C bile. We were particularly interested in comparing the C bile obtained at each of the two examinations. Where these estimations could be made it was observed that postinjection specific gravities were slightly *higher* than those of the controls—an average of approximately 0.5 point. It was noted that only in 5 instances did B bile appear after injections of Decholin in 1 or 2 of the 10-minute specimens, whereas in the controls it was present in 13 instances, continuing more or less

constantly through the examination. Thus it might be inferred that this chemical has a slight inhibiting effect on gall bladder emptying.

3. *Color.* The same difficulty that we encountered in our specific gravity evaluation arose in our color comparisons. The presence of B bile interfered with making any accurate inferences as to color response other than that the controls were generally darker than the postinjection returns.

4. *Type of Bile.* This feature of our experiments has been discussed in the two foregoing sections. B bile appeared in only 5 of the patients after injection, whereas it appeared in 13 during the control test. Two patients showed B bile on both tests in from 1 to 4 of the 10-minute portions of the returns.

5. *Blood Pressure.* In 2 patients the blood pressure rose slightly within the hour after injection. In 1 patient the systolic pressure rose 5 points and the diastolic 10 points; in the second patient the systolic pressure rose 10 points and the diastolic 5 points.

Nine patients showed a fall. This occurred usually at the first 30-minute reading after the injection, less frequently at 60 minutes and rarely as late as 90 minutes. When the primary fall was found at 30 minutes there was no further reduction, but it was fairly well maintained throughout the test and showed only a slight tendency to return toward the normal. The greatest fall in the systolic pressure was 32 points and the least 5 points. The average for the 9 patients showing a reduction of blood pressure was 21 points.

The diastolic pressure fall ranged from 5 to 23 points; average, 10 points. One patient had a fall of systolic pressure of 10 points and a diastolic rise of 5 points. In another the systolic pressure fell 5 points while the diastolic rose 20 points.

All blood pressure in the control experiments remained relatively constant, *i. e.*, none showed any appreciable tendency to fall or rise. Of all the patients the highest blood pressure was 130 systolic and 80 diastolic and the lowest was 80 systolic and 50 diastolic. This latter patient caused us a little apprehension as we gave the injection, but his pressure remained unchanged throughout the test.

6. *Pulse Rate.* Four patients had a rise of pulse rate averaging 5 beats. Seven had a fall, averaging 5 beats. In the other 10 patients the pulse remained constant. The highest pulse rate recorded throughout all the examinations was that of 100 in a man before injection, which fell to 94 at 30 minutes and was back to his normal of 80 at 90 minutes. It was presumed that nervousness, due to the approaching vein puncture, caused this change of rate. The lowest pulse rate was 68 before injection and remained so throughout the test.

7. *Untoward Effects.* (a) *Immediate* (while giving injection). Only 1 patient complained of lancinating pain in the upper right quadrant during injection, transitory in nature. There was,

however, a common complaint of bitter taste occurring in from 3 to 10 seconds after the injection was begun. This symptom disappeared within 10 seconds after the injection was completed. Those who at some time or other had vomited bile stated that the taste was that of bile.

(b) *Delayed* (two hours succeeding injection). One patient caused us some concern 10 minutes after the injection was completed. He developed a rapidly increasing edema of the face, to the extent that in 20 minutes from the time it began he was unable to open his eyes. Respiration and deglutition were unaffected. The conjunctival vessels were markedly injected and there was profuse lachrymation. The skin of the whole body was suffused and hot. There was tremor of the voice and hands, and he stated that he "felt dreamy." At the 90-minute period he was again normal, except that he felt weak. This patient's blood pressure fell 25 points for both systolic and diastolic during the first 30 minutes, but was back to normal at 90 minutes. The pulse rate rose 8 points at 30 minutes. This patient has a bad myocardium, and at 50 years of age his arteriosclerosis was marked. He had had long-standing gall tract disease with probable hepatic cirrhosis. During the test he returned 100 cc. and while on control he returned 30 cc.

Ninety minutes after injection, on arising, another patient complained of nausea and prostration. This was followed by vomiting. Four hours later she had severe cramp-like abdominal pains with foul, greenish diarrhea—20 stools within 24 hours. Thereafter there was a rapid subsidence and quick return to normal. In her case the diagnosis was cholecystitis with cystic duct catarrh.

(c) *Remote* (after 2 hours). One patient suffering with cholecystitis developed abdominal pain 48 hours after injection, with nausea and profuse salivation, continuing 48 hours. Another complained of burning pain along the course of the colon for several weeks. This was considered due to a preëxisting mucous colitis. In no instance was there any tendency to venothrombosis, phlebitis or cellulitis following intravenous injection.

**Conclusions.** From the above facts determined by our study it is evident that sodium dehydrocholate in 2-gm. doses intravenously increases the fluid return through the tube from the duodenum. We believe that this increase of flow is due to the extra amount of thin liver bile, which seems to be excreted in response to the administration of this chemical substance. We inferred, however, that this substance seems to inhibit the gall bladder emptying function. No effort was made to determine the effect on cholesterol excretion from hepatic or duct epithelium.

In approximately 50 per cent of patients there was produced temporary hypotension. There was no appreciable change in pulse rate. There were no particularly untoward effects, either immediate or remote, except in the two instances cited. We, therefore, believe

sodium dehydrocholate can be considered a nontoxic bile salt that can be administered intravenously with reasonable safety. In this report its therapeutic usefulness was not investigated.

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## A SURVEY OF DIPHTHERIA PREVENTION IN PHILADELPHIA.

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It is proper to consider immunity to diphtheria as a reason for failure to contract this malady. It is reasonable to assume that a highly immune population will have a lessened incidence and mortality from this disease. It is difficult to conceive of any survey that will give a mathematically accurate statement as to the actual immunity status in any large community. Practically every large city and many states have attempted to compile data that would show the progress made in establishing immunity to the disease by means of the administration of toxin-antitoxin or toxoid. Circuitous and complex methods have been employed by some agencies to obtain by cross section the immunity status of the nation. This has worked out to the satisfaction of some communities but has proved inaccurate in others.

Park and Zingher<sup>1</sup> established the proportion of naturally immune individuals that one might expect to find in given communities. These estimates have been verified by the author<sup>2</sup> and so many other observers in the past decade that they can be accepted without further reservation. That there has been no change in the natural

immunity status in the past 10 years is a matter of importance. It has not changed in the accepted childhood groups in Philadelphia. The almost universal decline in the incidence of diphtheria must be due, therefore, to some factor other than the natural immunologic status.

The early recognition of cases, their isolation, and the isolation of known carriers gave us an opportunity to estimate the value of these procedures and also showed us their fallacies long before active immunization against diphtheria was attempted. After a few years of experience with isolation one could hardly expect the precipitous decline in diphtheria incidence of the last few years. Case death rates have not declined to any great extent, consequently virulence has not materially changed. There has been no material or decided change in the percentage of diphtheria carriers recently in our communities, nor can the virulence of the organism be regarded as attenuated as a result of laboratory tests. The introduction of active immunization on a large scale has been followed by a precipitous decline in the incidence of diphtheria. It is necessary then to establish the relationship between active immunization and freedom from infection or to discover some other good and sufficient reason for diphtheria's decline.

A number of small towns, in a public-spirited fervor that one hopes will be a permanent feature of their community life, have immunized their children 100 per cent against diphtheria, with the result that no cases have occurred in their communities. In large cities any number of institutions have similar records, some of these institutions housing more children than the entire towns just mentioned. These observations would point the way to the necessity for wholesale active immunity in large communities.

Since the question has been raised that some communities have had a diphtheria decline with but a desultory effort at active immunization, it might be well to inquire into the facts concerning the accuracy of widely published statements to this effect. Some of these statements have been accredited to the highest authority and their statements are regarded as the acme of accuracy. For example, the White House Conference on Child Health has given estimates on the percentage of immunes in the infant and preschool group. Avidly accepted by the mass of medical and welfare groups interested in the study as accurate, they are not, at least in the instance of Philadelphia, anywhere near the demonstrable truth. Even as an indication of a trend, which was the real idea behind the compilation of these figures, they are disappointing since the student cannot find firm ground in them for the promulgation of logical thought. A real epidemiologic survey might reveal information that cannot be found at present concerning these communities. It is therefore pertinent that a large city give some statistical data regarding its work of immunization, its diphtheria case rate, and whatever might be of interest that would tend to establish a relationship between the two, or, on the other hand, contradict it.

Undoubtedly, the most important factor in the eradication of diphtheria would be the prevention of the disease in children below school age, since in this group occurs the largest number of cases. Table 1 shows the population of Philadelphia based upon the 1930 census.

TABLE 1.

Year.	Population.
1925 . . . . .	1,892,023
1926 . . . . .	1,904,431
1927 . . . . .	1,916,839
1928 . . . . .	1,929,247
1929 . . . . .	1,941,655
1930 . . . . .	1,954,063
1931 . . . . .	1,966,471

Table 2 gives the number of births occurring in the city of Philadelphia from 1925 to 1930.

TABLE 2.

Year.	Births.
1925 . . . . .	39,072
1926 . . . . .	38,646
1927 . . . . .	38,525
1928 . . . . .	36,903
1929 . . . . .	35,224
1930 . . . . .	35,548

This group shows that 225,918 children were born within the city limits and is therefore a reasonable estimate of our preschool age population. There should be deducted from this, however, 21,934 deaths, as indicated in Table 3, leaving a balance of 203,984 children, approximately 3000 or 4000 of whom really should not be included because of the fact that they are the offspring of people living outside the city limits who availed themselves of the facilities of Philadelphia hospitals.

TABLE 3.

Year.	Deaths from all causes in infants and children up to 6 years.
1925 . . . . .	4,308
1926 . . . . .	4,449
1927 . . . . .	3,379
1928 . . . . .	3,859
1929 . . . . .	2,952
1930 . . . . .	2,987

Immigration and emigration do not alter the actual number of children but are prone to reduce the number of immunes, so that the child population of Philadelphia of the preschool age group and under totals 200,984.

Every infant and child immunized by the Department of Public Health submits a signed written permission from its parents. On the reverse side of the permission blank space is provided for whatever treatment is given this particular child, together with the



date the treatment has been administered. This card is filled in at every visit by the physician performing the work. The cards of completed immunizations are filed in the main office of the Division of Child Hygiene. Incomplete or open cases are kept in the Center where the permission was originally given. Certificates of immunity are given to parents whose children have demonstrated that they have acquired immunity by reason of a negative Schick test performed 6 months or longer after the third injection of toxin-antitoxin. The following table shows the number of immunized children by years from 1926 to 1930.

TABLE 4.

Year.	Immunized children.
1926 . . . . .	8,861
1927 . . . . .	8,492
1928 . . . . .	26,990
1929 . . . . .	23,711
1930 . . . . .	28,198

This totals 96,252 children immunized by the Department of Public Health, of a group of 200,984 infants and preschool age children. This gives a percentage of 47.8 per cent of immunized children recorded in the Department files.

This percentage does not include children immunized by family physicians, hospitals not representing the Department of Public Health, and other independent welfare agencies. These sources have proved to be reluctant to supply accurate information concerning the extent of their work. This may be due to a failure to keep accurate records or a failure to realize the importance of accurate statistical data concentrated in a central point.

If we assumed that there were performed 5 completed immunizations by every physician in the city of Philadelphia in 5 years, discounting the welfare agencies and hospitals, a conservative estimate of approximately 12,000 additionally immunized children can be granted. It is conceded that a large proportion of physicians are specializing in the fields that do not come in contact with the preschool age child, so that the assumption that but one immunization per year per physician is a deliberately low estimate. This would bring the total of immunizations up to 53.8 per cent.

Hospital and welfare agencies could account for perhaps 1 per cent more, or in round figures a grand total of 55 per cent of the preschool age population is actively immunized against the disease. Of those children of preschool age receiving no immunization treatment, approximately 25 per cent are naturally immune, so that 66.25 per cent of the children of Philadelphia of the infant and preschool age group are immune to diphtheria.

The immunization of the school child has been carried on since 1925 and the following quotation from a communication written by Dr. Walter S. Cornell, Director of the Division of Medical Inspection of Public Schools, is illuminative:

"We know that of 97,810 children in the kindergartens and first three grades, 65,904 (67.4 per cent) were recorded as immunized, November, 1930. If we assume that the balance of the main group are 60 per cent immunized, we then arrive at a total figure of 143,292 pupils immunized out of the group of 226,795. This would be a proportion of 63.2 per cent.

"You may be interested in knowing the proportion of pupils immunized in our lower grades, as we have accurate information, and the disease diphtheria is most likely to exist in these lower groups. In November, 1930, we found 44 per cent immunized in the kindergartens, 61 per cent in grade one, 78 per cent in grade two, and 78 per cent in grade three. The figures increase with progress in the grades, because we repeatedly circularize the children until they are promoted out of the third grade, and thus each year we get a few children in the second and third grades who have heretofore refused to take the protective treatment."

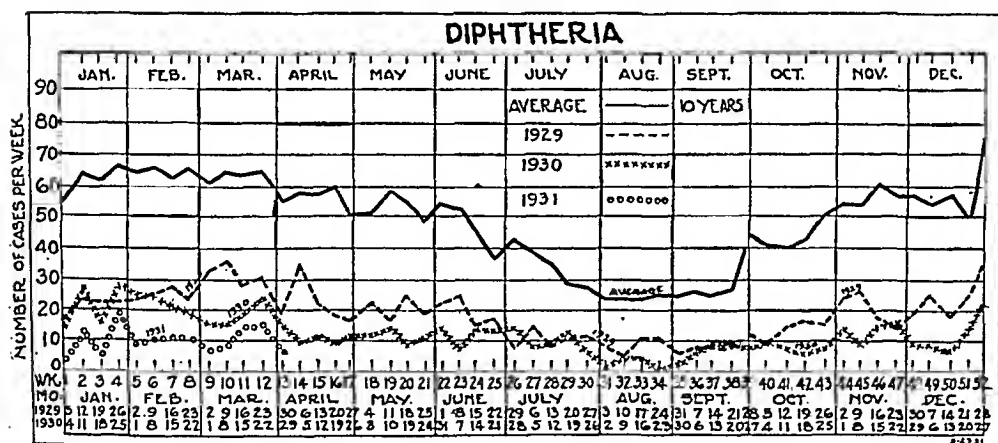
The incidence of diphtheria in Philadelphia will be noted as follows:

TABLE 5.

Year.	Case rate per 100,000 population.	Year.	Case rate per 100,000 population.
1919 . . . . .	207.9	1925 . . . . .	205.4
1920 . . . . .	184.0	1926 . . . . .	144.4
1921 . . . . .	183.6	1927 . . . . .	136.0
1922 . . . . .	165.5	1928 . . . . .	101.8
1923 . . . . .	177.3	1929 . . . . .	49.9
1924 . . . . .	206.1	1930 . . . . .	32.5

Table 6 is self-explanatory, as is also the chart:

CHART.



The number of cases of diphtheria occurring in the preschool age immunes in Philadelphia from 1925 to 1930, including the Department's children and those for whom immunity had been claimed but not proved, has been 40 cases. Of these, 21 cases occurred in

TABLE 6.—DIPHTHERIA FROM 1888 TO 1930, INCLUSIVE. Healthfax, November 25, 1929 2, No. 47.

Year.	No. of cases reported.	No. of deaths.	Case death rate.	Death rate per 100,000.	Year.	No. of cases reported.	No. of deaths.	Case death rate.	Death rate per 100,000.
1888	1,170	623	53.2	61.8	1910	3,804	492	12.9	29.08
1889	1,455	727	50.0	70.7	1911	3,792	498	13.1	30.37
1890	1,820	943	51.8	89.9	1912	3,080	388	12.6	22.85
1891	3,251	1,362	41.9	126.9	1913	2,626	359	13.7	20.59
1892	5,051	1,707	53.8	155.4	1914	2,610	329	12.6	19.97
1893	3,471	1,159	53.4	103.2	1915	2,613	317	12.1	18.71
1894	3,608	1,395	38.7	121.6	1916	2,499	390	15.6	22.7
1895	3,853	1,349	35.0	115.1	1917	3,141	441	14.0	25.64
1896	3,595	1,155	32.1	96.5	1918	2,477	384	15.5	21.9
1897	5,405	1,474	27.3	120.7	1919	3,763	445	11.8	24.15
1898	4,415	1,154	26.1	92.6	1920	3,368	413	12.2	22.74
1899	4,391	994	22.6	78.2	1921	3,382	318	9.4	17.36
1900	5,088	1,042	20.5	80.4	1922	3,069	281	9.2	14.83
1901	3,588	643	17.9	48.6	1923	3,310	270	8.1	14.04
1902	2,444	515	21.1	38.2	1924	3,874	275	7.1	14.09
1903	3,043	608	20.0	44.3	1925	3,887	315	8.1	16.1
1904	3,546	541	15.3	38.7	1926	2,750	266	9.6	13.55
1905	3,238	452	14.0	31.7	1927	2,607	220	8.4	10.81
1906	3,707	546	14.7	37.6	1928	1,964	230	11.2	11.1
1907	3,840	509	13.3	34.5	1929	969	89	9.18	4.25
1908	3,863	496	12.9	33.1	1930	635	48	7.55	2.46
1909	3,878	512	13.2	33.5					

The dispensing of antitoxin began in 1896.

the group of 96,252 children for whom the Department of Public Health claimed immunity.\* Diphtheria in the preschool age group covering the period of this survey can be divided as follows:

	No. of cases.	Per cent.
Immunes . . . . .	40	0.8
Nonimmunes . . . . .	4872	99.2
Total . . . . .	4912	

This extremely small number of cases among immunes would represent the human element of error in the interpretation of Schick reactions, and the number is insignificant as compared with the number of cases occurring from 1926 to 1930 inclusive.

The immunizations in the public schools were done on an intensive scale from 1925 to 1927 inclusive. The tables show a significant upward trend in the latter years, the preschool and infant age approaching the school immunization percentages. If the school-age child has been immunized beyond the recognized percentage proportions over the earlier age groups, then the number of cases should show a percentage increase in the least protected group.

Table 7, page 846, will show the cases arranged according to age and the percentage in each group.

At a glance it can be seen that the proportions, beyond reasonable fluctuation, have not changed, but the actual incidence has decreased.

One important factor must again be emphasized, that if active immunization is not effective in stamping out diphtheria, then the number of cases, whether the totals are decreased or not, should be proportionately divided between those so immunized and those not immunized, as expressed in their age groups. This is obviously not the case and the record of over 96,000 children must be considered.

**Summary.** Approximately 55 per cent of the children of infant and preschool age have been immunized against diphtheria in the city of Philadelphia, 47.8 per cent of whom have been immunized by the Department of Public Health; 66.25 per cent of the children of this age group and perhaps more of the school age group have either been immunized or are naturally immune to the disease. The incidence of diphtheria, since these figures have been attained, has been reduced 80 per cent. Ninety-nine and two-tenths per cent of the cases occurring in the city of Philadelphia occur in non-immunized children or in those in whom no immunity has been demonstrated. Less than 1 per cent of cases occurred in immunes.

\* NOTE.—Covering the period of this survey 26 infants and preschool age children developed diphtheria in the Department's group of toxin-antitoxinized children before they had passed the period of immunity development: 24 were reported as being recently injected by private physicians. Since 11 per cent of our series require further immunization at the end of 6 months, these cases hardly indicate an increased primary phase (negative phase) susceptibility by reason of toxin-antitoxin administration.



Bacteriologically, the disease is as virulent as ever, and the death rate carries on the even tenor of its way. No other new epidermiologic factor except active immunization with toxin-antitoxin has been utilized to combat the spread of infection and the older methods are as inadequate as ever. Destiny's finger seems to point definitely to active immunization as the weapon with which to combat and eradicate diphtheria.

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### CLINICAL OBSERVATIONS ON THE SO-CALLED LEATHER-BOTTLE STOMACH.\*

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LEATHER-BOTTLE stomach is a term which has been attached to a number of conditions in which the stomach is contracted to that of a small organ of diminished capacity, and in which the walls are thickened rigid and present an entire loss of flexibility. Much confusion still exists regarding its actual significance, for although from a macroscopic viewpoint the general appearance of the stomach is the same, yet on close observation it presents various different lesions. Further confusion has arisen by the application of such terms synonymously as "linitis plastica," cirrhosis and sclerosis of the stomach as well as leather-bottle stomach.

The leather-bottle type of stomach was first described, by Andral<sup>1</sup> in 1834 and a condition recognized by Cruveilhier<sup>2</sup> in 1839, in which a special type of irregular hypertrophy of the stomach was present at and some distances beyond the pylorus with definite involvement of the submucosa. It remained, however, for Brinton<sup>3</sup> to name the

\* Presented by title at the Meeting of the Association of American Physicians at Atlantic City, May 6, 1931.

disease "linitis plastica," and more fully to point out the pathologic changes occurring in the stomach in this affection, emphasizing especially its inflammatory state. Since then, the cancerous nature of this affection has been stressed by some and the chronic inflammatory by others, while it has been further suggested by Bensusan and Rivet,<sup>4</sup> as well as Lewald,<sup>5</sup> that it may even develop upon the basis of a syphilitic lesion of the stomach.

This lack of unanimity is largely due to the interpretation placed upon the pathologic processes. As has already been pointed out, a number of varied pathologic conditions may produce identical appearances in the gross specimens and unless careful microscopic investigations are undertaken, erroneous conclusions may be reached.

Wyand<sup>6</sup> has clearly presented this problem in a table, which we have taken the liberty of slightly modifying.

Leather-bottle stomach	$\left\{ \begin{array}{l} 1. \text{ Carcinoma} \\ 2. \text{ Fibromatosis} \end{array} \right.$	$\left\{ \begin{array}{l} \text{Diffuse} \\ \text{and} \\ \text{local} \\ \text{Diffuse} \\ \text{and} \\ \text{local} \end{array} \right.$	$\left\{ \begin{array}{l} A. \text{ Sclerosing carcinoma or carcinoma} \\ \text{plastica (improperly called linitis} \\ \text{plastica).} \\ B. \text{ Other forms of carcinoma.} \end{array} \right.$

The difficulties encountered in differentiating these varied affections can be best recognized by a study of the individual pathologic processes.

**Sclerosing Carcinoma, So-called "Linitis Plastica."** This lesion may present one of two types, either localized surrounding the pylorus or a diffuse involvement of the entire organ. The second is the final stage of the local disease. A very rare form of carcinoma plastica has been described in which various other regions of the stomach have become involved in localized patches. As a result of the increase in connective tissue and thickening of the gastric wall, especially of the submucous layer, a diminution in size of the stomach is produced, leading to as small a capacity as 100 cc.

In the areas involved, the wall of the stomach is contracted and presents an entire loss of flexibility, is rigid and thickened and hard in consistency. The process takes its origin at the pylorus and progresses gradually toward the cardia in its involvement of the entire stomach. If the pylorus is alone involved, stenosis with dilatation of the stomach may be produced. The peritoneal coat presents a pearly white, dull appearance and not infrequently adhesions will be observed between the stomach and neighboring organs.

In its final stages, the stomach is sausage-shaped and greatly diminished in size, at times but 6.5 cm. to 7.5 cm. by 3.5 cm. and is thus converted into a rigid tube. The thickening ordinarily only involves the stomach itself and does not extend beyond into the duodenum, though a number of observations in which the intestines



FIG. 1.—Carcinoma plastica. (Courtesy of Dr. Allan J. Smith. From Rehfuess, Diseases of the Stomach, W. B. Saunders Company, publishers.)

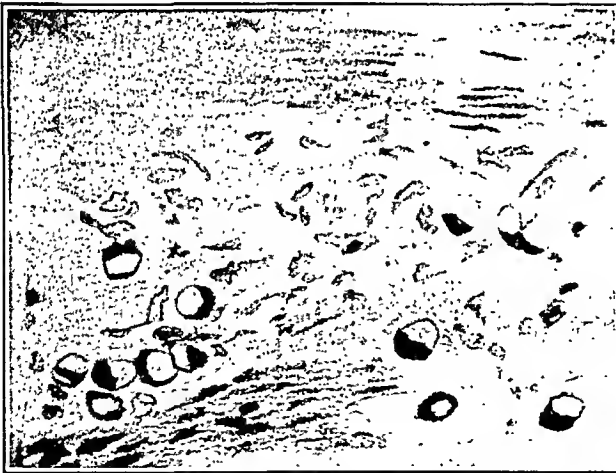


FIG. 2.—Section of stomach wall in region of pylorus showing signet-ring cells. (From Aaron and Wadsworth.)





FIG. 3.—Illustrates the roentgenogram of a case of leather-bottle stomach. Note the tubular, narrowed contracted stomach.

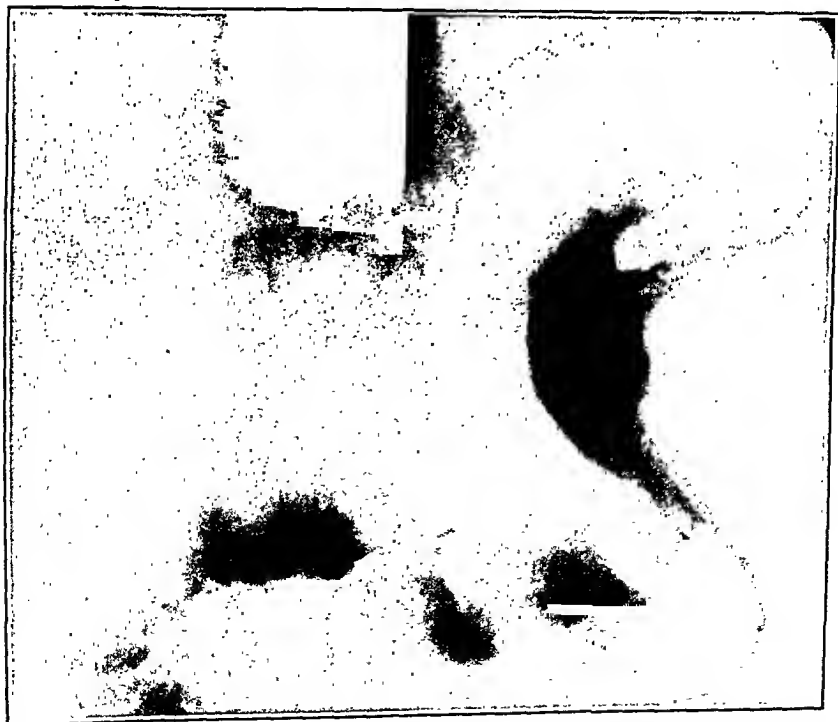


FIG. 4.—Shows another case of a markedly contracted stomach, diagnosed as leather-bottle stomach, and confirmed by operation.

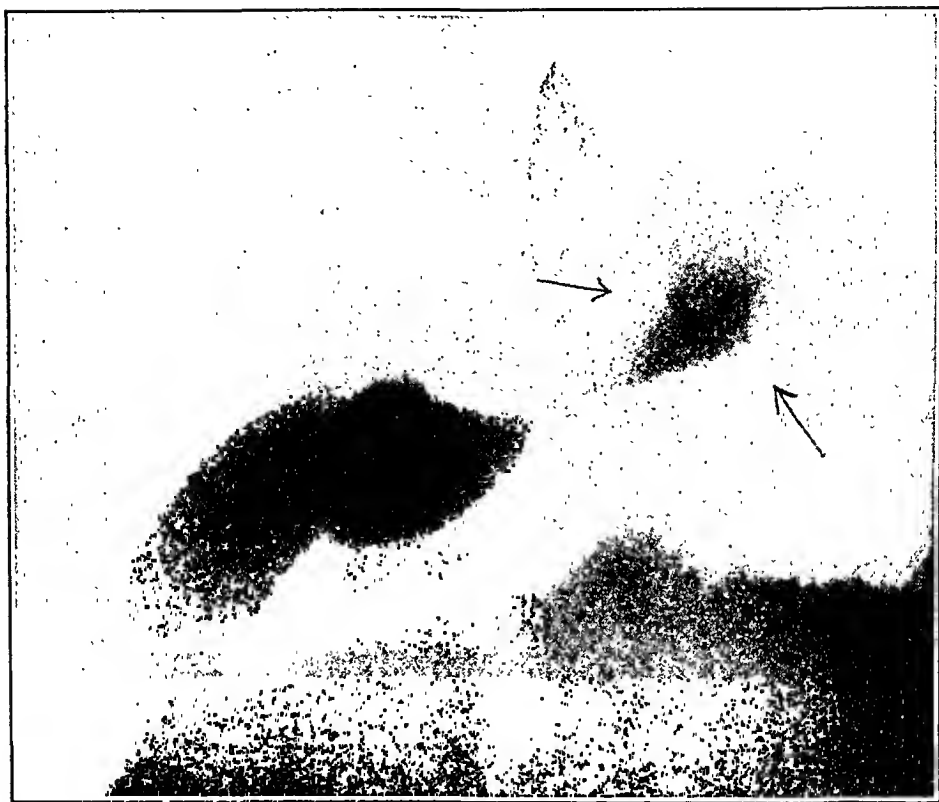


FIG. 5.—Roentgenogram showing the tubular effect of the entire stomach, in a case of leather-bottle stomach. This represents the immediate view, and reveals the markedly rapid emptying of the stomach.

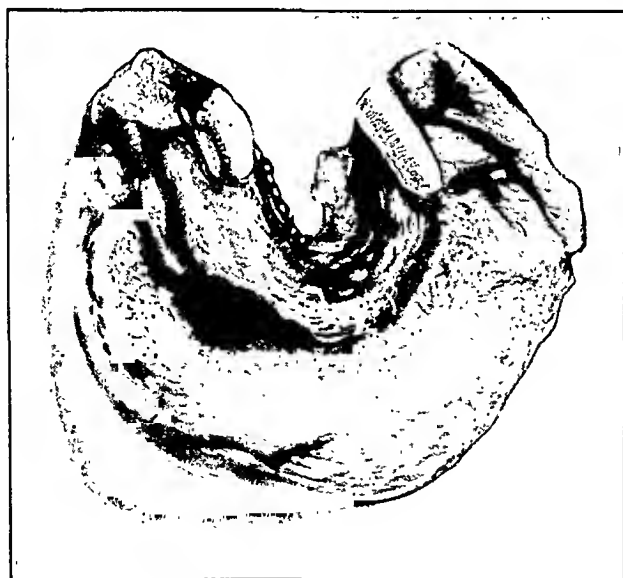


FIG. 6.—Leather-bottle stomach spread out showing partly opened lumen (fibromatosis type); autopsy specimen.



FIG. 7.—Roentgenogram of a small contracted stomach, which emptied with marked rapidity.

and other viscera were involved in a similar process have been recorded. Glandular involvement is not unusual. It was present in 15 of the 23 cases of Lyons.<sup>7</sup> According to Wyard<sup>6</sup> the glands may be hard, suggesting malignant infiltration, yet this is not always confirmed by microscopic examination. In a single instance of Baumgartner's, Cases' and Deegan's<sup>8</sup> 5 cases, cancerous involvement of the greater omentum was noted. On section, the various layers of the stomach may be recognized, though not nearly as definitely as under normal conditions. These are much thickened to the greatest degree at the pylorus and least at the cardia. The mucosa not infrequently presents a wrinkled appearance and is thrown into folds produced by the contraction of the other layers. The rugæ are often diminished in number and flattened and the mucosa itself may become entirely obliterated in certain areas. The greatest thickening is due to the increase of connective tissue in the submucous layer which may attain from 10 to 15 times its normal thickness, is white in appearance, and is hard and firm on section. This layer constitutes a large portion of the gastric wall. The muscular layer presents glistening fibrous bands with segmentation of the circular muscles by the fibrous tissue. The longitudinal muscles are only involved in the late stages of the disease. Interfibrillary infiltration of the muscle is absent to a great degree and there is but slight actual destruction or invasion of the muscular layer, connective tissue being present only between the muscular bundles.

Ulceration is not infrequent; it was present in but 5 (22 per cent) of the 23 cases of Lyons<sup>7</sup> which, however, is not in accord with the findings of Thomson and Graham<sup>9</sup> who observed it in 7 of 9 specimens (77 per cent).

On microscopic examination, the mucosa may present a normal appearance in certain areas with abundant secretion of its glands and increased discharge of mucus; in others degenerative changes in the cellular structure are noted, produced as the result of the interference with the blood supply by the contracting fibrous tissue. The submucosa is greatly thickened and represents at least a half of the increase in the gastric wall. Connective tissue fibers may be observed invading the muscular coat from the submucosa into the subserous and serous structures, interlocking one another and surrounded by numerous small bloodvessels. These fibers are not uncommonly nucleated. The muscularis is hypertrophied and interlaced with connective tissues extending from the submucosa. A thickening of the subserous coat due to the connective tissue increase is also noted.

In all of the coats of the stomach, but more especially in the submucosa in addition to the nucleated connective tissue cells already referred to, there are present numerous small cells containing irregular nuclei of varying size. These may occur singly or in groups and

resemble epithelial cells. Aaron and Wadsworth<sup>10</sup> give the following description of these cells: "Their cytoplasm is usually clear with no distinct membrane or is frequently represented by a large vacuole surrounded only by what appears to be a cell membrane. Within the vacuole a small globular mass staining deeply with eosin can be seen. These vacuolated elements usually have their nucleus pushed to the extreme periphery where it appears like a thickening of the membrane, giving the cell the form of a signet ring. These peculiar cells are found not only in the submucosa, but also in the connective tissue patches of the muscularis in the neighborhood of bloodvessels, where they often seem closely packed together.

"These elements have a decided degenerated character as is evidenced by their shapeless nuclei, structureless confluent chromatin and the vacuolization of their cytoplasm. From the staining reactions of the latter with hemotoxylin, it seems possible that the degenerative changes in the cytoplasm are of a mucoid nature. The nature of these cells cannot be definitely ascertained, yet they are strongly suggestive of epithelial cells found in certain forms of carcinoma of the stomach, especially the so-called Krukenberg carcinoma." (Figs. 1 and 2.)

The presence of pure mucin has been demonstrated by Reynier and Masson<sup>11</sup> in these epithelioid cells by means of specific stains. It is not clear according to Vecchi<sup>12</sup> whether these cells represent epithelial cells in mucoid degeneration or whether the cells secrete mucus and assume this peculiar tendency, due to the resistance produced by the connective tissue to the invasion of the cells.

According to Ewing<sup>13</sup> this type of carcinoma must distinctly be differentiated from the usual scirrhus cancer of the stomach in which with the diffuse thickening of the coats there is evidence of metastases as well as the presence of the usual carcinomatous cells. In carcinoma plastica there is on the other hand, a diffuse scanty infiltration of large cells with hyperchromatic nuclei and only slight tendency to metastasize. From a careful review of the literature, the evidence is becoming more and more convincing that "so-called linitis plastica," though formerly viewed in the light of a chronic inflammatory process, is now fairly well established as a carcinomatous process. It should therefore be dropped as a misleading term. While it may still be extremely difficult at times to interpret the epithelioid cells as carcinoma cells, yet evidence in this direction is constantly increasing. So eminent a pathologist as Ewing has definitely accepted this view, based on the fact that following a diligent study of his specimens, he has never failed to find the epithelioid cells with mucous degeneration and signet-ring nuclei as undoubted evidence of carcinoma. It is unquestionably true, that many of the earlier cases were studied imperfectly; for Curtis,<sup>14</sup> who in a report described a case as noncancerous, after a restudy of many sections was finally able to demonstrate cancer cells. How-

ever, the problem still remains complicated, since extremely careful histologic studies are always required to definitely establish the diagnosis. Nevertheless even in the absence of definite elements in the sections obtained it is not possible always to rule out malignancy nor does the absence of glandular metastases necessarily indicate malignancy of the so-called linitis plastica type.

**Other Forms of Carcinoma of the Stomach.** Aside from the cases of carcinoma plastica of the type already described, there are instances of carcinoma of the stomach from which these are clinically indistinguishable. These cases may present a local or diffuse involvement and may be according to Wyard<sup>6</sup> of the scirrhus, cylindrical cell or colloid type. Of these, the diffuse scirrhus variety is most common. This form of carcinoma is not usually difficult to distinguish from "carcinoma plastica" by the diffuse thickening noted equally in all of the coats of the stomach; the presence of unquestionable and easily distinguishable carcinoma cells as well as by metastases. The stomach in these cases is contracted and smaller than normal; the surface being roughened by the presence of numerous small nodules and the lumen is of diminished capacity. The mucous membrane is markedly involved and destroyed with the production of irregular indurated ulcerations. Wyard reports 3 instances of leather-bottle stomach due in one instance to a scirrhus, in another to a cylindrical cell and still another to colloid carcinoma.

**Fibromatosis or Cirrhosis of the Stomach.** There are undoubted instances of leather-bottle stomach of benign origin. They may occur in the local or diffuse form. Auneau,<sup>15</sup> Tassin<sup>16</sup> and Maier report cases of hypertrophic stenosis of the pylorus closely related to this condition. Henry and Osler<sup>18</sup> described a form of diffuse cirrhosis due to a chronic gastritis leading to atrophy of the stomach with features of pernicious anemia. Krompecker and Makai<sup>19</sup> recognize cases of the diffuse type attributed to chronic inflammation, the changes in the stomach being produced by fibrosis and muscular hypertrophy associated with edema. In Lyle's<sup>20</sup> most complete review of the literature of this subject, 68 cases of the benign variety of this condition are recorded. His own cases in which a gastroenterostomy was performed proved to be benign from the sections of the tissue removed and from the fact that the patient lived 11 years following the operative procedure. Bland-Sutton<sup>21</sup> considers the changes occurring in the stomach in this condition in the same light as that observed in the atrophic gall bladder in cholecystitis. As the result of an ulcer of chronic gastritis changes are produced leading to a cirrhosis of the stomach. In Wyard's<sup>6</sup> report, 2 instances of the local variety and one of the diffuse are noted, and Dwight<sup>22</sup> records two of the diffuse type.

Diffuse fibromatosis may have its origin as a local manifestation becoming progressive and finally may invade the entire stomach.

When the stomach is completely involved, it presents the typical picture of the leather-bottle stomach. The stomach at this stage is firm, greatly diminished in size and sausage-shaped. The lumen is narrowed and the pylorus usually contracted. The mucous membrane is largely replaced by the hypertrophied submucosa producing small nodular protrusions into the lumen. While the mucous membrane is largely destroyed, the submucous and muscular layers are much thickened by connective tissue growth and many of the muscular elements destroyed. At certain areas they are hypertrophied. The peritoneal coat becomes but slightly involved.

Microscopically, the walls of the stomach are found much thickened due to the increase of connective tissue; much of the mucosa has vanished, the remaining portion presenting a swollen appearance with edema. The glands are largely destroyed but in those areas in which they still persist, the epithelium is desquamated. The submucosa is largely replaced by connective tissue through which numerous fibroblasts and bloodvessels can be distinguished. These fibers extend irregularly in all directions. The muscular coat is also filled up with connective tissue which invades this area destroying many of the muscle fibers. Many of the latter show vacuolization with disappearance of their nuclei.

The following histories illustrate the various types of leather-bottle stomach:

*Leather-bottle Stomach of the Carcinoma Plastica Type. Case Reports.*  
 CASE 1.—E. K., a woman, aged 22 years, complained of vomiting with which she had been affected about 4 weeks and which continued daily together with acid eructations, pain in the abdomen and marked constipation. There had been considerable loss of weight. The patient was much emaciated. Nothing abnormal was detected on examination of the abdomen. The gastric contents revealed an achylia; total acidity, 10; free HCl, 0. A Roentgen ray examination of the gastrointestinal tract disclosed an extremely small vertical stomach with pyloric stenosis and marked retention. On account of the decreased size of the stomach with gastric retention the diagnosis of carcinoma plastica was considered. An operation was performed by Dr. McGlannan who found a very small contracted stomach with a narrow pylorus, which scarcely admitted the tip of the little finger. The wall of the stomach was 15 mm. in thickness, each layer showing distinctly, the muscular coat presenting the glistening fibrous bands. The mucous membrane itself appeared rather thin and the fibrous bands from the submucous layer showed up distinctly. A posterior gastroenterostomy was performed. Dr. McGlannan was definitely of the opinion that this case represented an instance of the carcinoma plastica type of the leather-bottle stomach though no pathologic study was available. The patient made a satisfactory recovery as the result of the operative procedure, gained in weight and strength for a period of nearly 4 years. She then began to lose flesh rapidly, gave indications of an extreme degree of anemia and died within 6 months. Since no pathologic examination was possible it is difficult to state definitely whether this case represents a carcinoma of the plastica type of leather-bottle stomach or the usual scirrhus form. The extremely small stomach, however, with the absence of metastases and the long duration of the disease rather tends to indicate that the type is probably one of carcinoma plastica.

*Leather-bottle Stomach of the Scirrhus Carcinomatous Type.* CASE 2.—W. H. K., female, aged 47 years, had complained for about a year of fullness in the stomach and regurgitation of food following meals. This condition had become greatly aggravated and was accompanied by excessive formation of gas and nausea but not with vomiting. The patient lost 82 pounds in weight during this period.

On physical examination the marked loss of flesh was evident. The abdomen was soft, extremely relaxed and a suspicious mass was palpable in the left upper quadrant of the abdomen, sausage-shaped and tender on pressure. The gastric analysis revealed an achylia; total acidity, 35; free HCl, 0. The Roentgen ray report of the stomach was as follows: Stomach is small, in normal position, tubular and sausage-shaped, cardiac orifice is irregular, and the motility is very rapid, the stomach being almost empty in 10 minutes. There is a distinct absence of peristaltic waves. Examination of the gall bladder by means of the oral administration of tetraiodophenolphthalein shows a large negative shadow.

The diagnosis of leather-bottle stomach of the carcinomatous type together with cholelithiasis was made. The patient continued to lose weight and strength, the digestive symptoms becoming more pronounced and she died after a few months as the result of a terminal pneumonia complicated by extensive malignant disease with metastases in the liver. (Fig. 3.)

The sudden appearance of the digestive symptoms in a patient of middle life with a rapid loss in weight and downward course and the presence of an epigastric mass associated with a nodular liver together with the finding of an achylia as well as Roentgen ray evidence seem to justify the conclusion that we are dealing with a carcinoma probably of a scirrhus type.

*Leather-bottle Stomach of the Scirrhus Carcinomatous Type.* CASE 3.—A. T., a man aged 46 years, had been subjected to digestive upsets, in the form of pressure, fullness, distention and constipation for years. There had never been any pain. During the last year the patient had frequently been nauseated but had not vomited until within the last few months. Since then, this symptom has become aggravated and is preceded by extreme nausea and epigastric pain. The patient has lost 25 pounds in weight during the past 3 months.

On physical examination, aside from the evident loss of flesh nothing of importance was revealed. The abdomen was soft, the liver was slightly enlarged and tender to pressure and the inguinal glands were somewhat enlarged. The gastric contents after an Ewald test meal showed a total achylia. A Roentgen ray examination disclosed a small left-sided stomach one-third the normal size. The diagnosis of leather-bottle stomach was made and operation advised. On opening the abdominal cavity, numerous hard nodular masses as large as a pea, and some even larger, were detected studding the peritoneum and omentum. The stomach was small, about one-third its normal size. A hard indurated mass enveloped the pylorus, extending as far up as the center of the greater curvature. The condition was definitely malignant and represented the carcinomatous form of leather-bottle stomach. The patient recovered from the effects of the operation but died 3 weeks later. (Fig. 4.)

The operative appearance of the lesion in this case together with the widespread metastases throughout the peritoneum and omentum strongly suggested the presence of a scirrhus carcinoma in this patient. Unfortunately no specimen was removed at the operation so that no sectional study was made to classify this case positively.

*Leather-bottle Stomach of the Scirrhus Carcinomatous Type.* CASE 4.—R. L. E. T., a female, aged 56 years, consulted us 6 weeks following the discovery by her family physician of a "serious trouble with her stomach"



during a complete examination for "neuritis." The patient presented no symptoms of gastrointestinal disease but due to the advice given her became rather alarmed and worried and lost about 15 pounds in weight. The only positive finding on physical examination was an indefinite sausage-shaped mass palpable mainly to the left of the umbilicus and below it. The lower pole of the right kidney was palpable but the liver was not enlarged and no tender areas could be detected. The laboratory tests, including the Wassermann reaction, blood chemistry and picture, revealed no abnormalities. A fractional gastric analysis disclosed a true achylia. The Roentgen ray examination showed a small fish-hook stomach with a slight deformity in the pyloric region suggesting an ulcerative lesion. The colon was prolapsed and there was an 18-hour retention present in the terminal ileum. The diagnosis of carcinoma of the stomach was made and an exploratory laparotomy urged. At operation a small stomach with a marked thickening of the pyloric third was found. A little more than the pyloric third of the stomach was removed and an end-to-end anastomosis was performed. On incising the resected portion of the organ no ulceration of the mucosa was noted, but there was considerable thickening of the sub-mucous and muscular coats. On microscopic examination the sections showed a scirrhus carcinoma. The patient made an uneventful recovery. When last heard from 2½ years following operation, she was still in good health. This is an example of a leather-bottle stomach of the scirrhus carcinomatous type with a 2½ year's cure following resection.

*Leather-bottle Stomach of the Scirrhus Carcinomatous Type.* CASE 5.—G. C. F., a male, aged 24 years, complained during the past 5 months of loss of weight (50 pounds), difficulty in swallowing, fullness, and discomfort following meals and occasional nausea and vomiting. Up to the onset of his present trouble, he had always enjoyed good health. His physical examination aside from the evident emaciation revealed nothing of importance. The abdomen was generally quite sensitive to pressure but no definite masses and no enlargement could be detected. The laboratory tests were negative except for the presence of a true achylia gastrica. A Roentgen ray examination revealed a definite obstruction to both the liquid and breaded meal at the cardiac orifice of the stomach, there was also a narrowing in this region but no defects were noted. The stomach occupied a high position; it emptied rapidly due to a patency of the pylorus and showed a marked deformity over its entire length presenting an irregular tubular appearance suggesting a leather bottle stomach of the malignant type. An esophagoscopic examination disclosed a narrowing at the lower end of the esophagus but there was no evidence of malignancy.

At operation a leather-bottle stomach was found together with a general carcinomatosis involving the liver, mesenteric glands and peritoneum. A section of a resected gland revealed the presence of a scirrhus carcinoma. Following operation the patient rallied for a few weeks and was able to partake of a small amount of liquid nourishment but gradually weakened more and more, continued to lose weight and died 4 weeks later. (Fig. 5.)

*Leather-bottle Stomach of the Fibromatosis Type.* CASE 6.—I. P., a woman, aged 56 years, complained of indigestion at various times for a number of years; during the past 5 months her symptoms had become aggravated and there had been considerable nausea, vomiting, eructations, discomfort and pain at times following meals, together with a marked loss of appetite. She had lost 35 pounds in weight during the past few months. On examination the patient was found much emaciated, the abdomen was soft but no masses or tender areas could be detected. The gastric contents presented a total achylia with considerable amounts of lactic acid. A Roentgen ray examination could not be undertaken as the patient seemed too ill. A diagnosis of carcinoma was made notwithstanding the absence of a palpable mass.

At operation, the stomach was found extremely small, not larger than the size of a fist, nonadherent and the wall thick and rigid. The pylorus was much contracted. The patient was so badly shocked that further surgery had to be abandoned and the abdomen was closed. It was quite evident that we were dealing with a case of leather-bottle stomach. She died within 2 days as the result of shock. At autopsy, a very small stomach was found measuring 8 cm. by 4 cm. The stomach wall was much thickened, the mucous membrane was thin and denuded; the strings of white fibrous tissue appearing through the mucosa. The muscular layer revealed the glistening fibrous bands especially marked. The pylorus was so contracted that an ordinary probe could only be forced through with difficulty.

On microscopic examination the mucous membrane was found largely denuded, the submucous and muscular layers being much thickened by connective tissue growth and many of the muscular elements destroyed. The glands had disappeared to a marked degree but in those areas in which they still remained, the epithelium was desquamated. No evidences of malignancy could be detected. (Fig. 6.)

*Leather-bottle Stomach of the Fibromatosis Type.* CASE 7.—R. E. C., male, aged 41 years, consulted us for indigestion which first manifested itself 17 years previously. This consisted mainly of pain and distention following the ingestion of food. Sixteen years ago an appendectomy was performed without great relief. Upon a dietetic and medicinal regimen the patient managed to remain fairly comfortable for 5 years when similar symptoms of greater severity recurred. A diagnosis of duodenal ulceration with mucous colitis was then made and his symptoms were somewhat controlled with belladonna, alkalies together with frequent feedings. Recently, notwithstanding these measures, the distress has become markedly aggravated.

The examination now reveals an obese abdomen with a slight enlargement of the liver and an exquisitely tender area in the midepigastrium. The laboratory tests presented no abnormalities with the exception of the presence of a true achylia. The Roentgen ray investigation showed a retardation of the barium meal at the cardia but no definite obstruction was observed even following a breaded meal. The stomach appeared strikingly small, was of the cow-horn type, high position but showed no defects although the pylorus appeared somewhat narrowed. The peristaltic waves seemed obliterated and the meal flowed rapidly through a gaping pylorus. The duodenal cap could only be visualized with difficulty and appeared somewhat flattened and directed posteriorly up under the gall bladder region. The presence of a small irregular stomach with symptoms of long duration and subsequent course suggested a leather-bottle stomach of the fibromatosis type. (Fig. 7.)

**Etiology.** The etiology of the leather-bottle stomach of the carcinoma plastica, as well as of the scirrhus type, is necessarily unknown. On the other hand, such conditions as syphilis, alcoholism, cardiovascular disease, chronic gastritis have been considered as causative factors in the fibromatosis form.

Leather-bottle stomach occurs usually in adults. Of Lyle's<sup>20</sup> 126 cases, the largest number occurred between the 40th and 60th years. The average age of the 38 cases of Lyons<sup>7</sup> was 52 years. The disease is about twice as frequent in males as females.

It was observed in 3 males and 4 females in our series; the ages ranging from 22 to 56 years.

**Symptomatology.** The symptoms closely resemble those of carcinoma of the stomach. The onset may be abrupt or may be preceded by vague signs of indigestion. At first the symptoms are usually mild, consisting of anorexia, eructations and discomfort in the upper abdomen. These soon become more pronounced and are accompanied by fullness following small quantities of food, vomiting, abdominal pain, progressive loss of weight and strength as well as marked anemia. The pain is frequently of the ulcer type, that is, relieved by food and alkalis.

According to Carnot<sup>23</sup> when the pyloric sphincter is not involved in the process, it remains in a state of continuous contraction and inasmuch as the stomach can only hold but small quantities, food is ejected as rapidly as it is consumed, often presenting the picture observed in carcinoma at the cardia. If the pylorus, is however, involved it remains relaxed and the contents of the stomach pass rapidly through the orifice which continues unless stenosis is finally produced.

On physical examination an epigastric mass can usually be palpated which is hard but rarely tender. At times in advanced stages, the mass can be detected as a movable sausage-shaped tumor. A mass of this type was noted in but 2 of our 7 cases.

The gastric analysis usually reveals an achlorhydria. Of 30 of Lyons'<sup>7</sup> cases in which the gastric contents were examined, free hydrochloric acid was absent in 22 and but 8 had free hydrochloric acid ranging from 6° to 32°. Lactic acid has been noted in a few instances. A true achylia was present in all of our 7 cases.

**Diagnosis.** The Roentgen ray presents the best method of determining the presence of leather-bottle stomach. The stomach usually empties extremely rapidly in the diffuse form, appearing in the films as a narrowed tube with sharp outline. There is an entire absence of peristalsis. A filling defect is often observed involving a large area of the stomach. In the local form the pylorus is found narrowed and presents definite evidence of obstruction. There are no Roentgen ray signs differentiating carcinoma plastica from other forms of leather-bottle stomach; the picture is often not unlike that of other forms of cancer of the stomach. In fact, the diagnosis before operation is usually carcinoma; in one of Baumgartner's<sup>8</sup> cases it was ulcer. In Lyle's<sup>20</sup> report of 126 cases the diagnosis was only correctly made in 2 instances. The diagnosis of leather-bottle stomach should be considered in adults who present a sausage-shaped mass in the epigastrium, a true achylia, loss of flesh and the suggestive Roentgen ray signs referred to above.

**Prognosis.** The duration of life in leather-bottle stomach varies greatly according to the type of lesion. In the 33 cases reported by Lyons' the average duration was 23 months, the longest 15 years, the shortest 5 weeks. The average loss of weight was 21 pounds.

In Baumgartner's<sup>8</sup> series of 4 cases, duration of symptoms extended over a period of 1 year; in ours, from a few weeks to 17 years.

The symptoms of leather-bottle stomach are progressive, pyloric stenosis is common and unless surgical measures are instituted death occurs as the result of anemia, inanition, metastases and cachexia.

**Treatment.** This is definitely surgical. Until this procedure can be undertaken, the patient should be given small, frequent, easily digestible meals. If the pyloric obstruction is not too marked, duodenal feeding is indicated. In the light of our present knowledge of achylia gastrica in its relation to pernicious anemia, the question arises as to the value of liver feeding or ventriculin as a means of improving the general nutrition of the patient.

Sooner or later, unless operation is undertaken, the disease will prove fatal. Pylorotomy or gastrectomy are the operations to be recommended whenever possible. Occasionally, gastroenterostomy has been performed. Of Lyons'<sup>7</sup> 33 cases at The Mayo Clinic, in which 15 explorations, 3 gastroenterostomies and 15 resections were performed, there were 6 operative deaths. Of the 27 patients surviving operation 21 were dead.

**Conclusions.** From a study of our cases as well as those recorded in literature, the following conclusions may be drawn.

1. The term "leather-bottle stomach," as suggested by Wyard, should be reserved as a general term for a number of conditions which though similar in gross appearance, present, however, a varied pathology. Clinically, it is rarely possible to differentiate these types.

2. This condition may present a local or diffuse involvement.

3. The term "linitis plastica" should be discarded and a more appropriate term such as "carcinoma plastica" be substituted. This is represented by a small-cell epithelioid growth, having definite pathologic characteristics, the diagnosis of which cannot be made except following a most painstaking microscopic examination.

4. The clinical as well as Roentgen ray manifestations of leather-bottle stomach are similar, no matter what the characteristic pathologic changes may represent. These manifestations are largely those of carcinoma though there appears to be a type which is definitely not malignant.

5. The carcinoma plastica and fibromatosis forms produce death by inducing profound anemia and malnutrition; the scirrhus carcinomatous type largely as the result of metastases.

6. The treatment is surgical; the only hope for a complete cure lies in radical surgery, either in the form of pylorotomy or gastrectomy. Occasionally palliative measures as gastroenterostomy may afford relief.

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## REVIEWS.

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FRACTURES OF THE JAWS. By ROBERT H. IVY, M.D., D.D.S., F.A.C.S., Professor of Maxillo-facial Surgery, Graduate School of Medicine, and of Clinical Maxillo-facial Surgery, School of Dentistry, University of Pennsylvania, and LAWRENCE CURTIS, A.B. M.D., D.D.S., Assistant Professor of Maxillo-Facial Surgery, Graduate School of Medicine, and School of Dentistry, University of Pennsylvania. Pp. 180; 177 illustrations. Philadelphia: Lea & Febiger, 1931. Price, \$4.50.

THE authors of this book are so well known from their previous publications and demonstrations on fractures of the jaws that their monograph may well be considered as authoritative on this subject. After thoroughly considering the anatomy of the parts and the symptoms and signs of fractures, a detailed discussion is given of the manner by which these fractures may best be handled.

The approved methods of treatment of fractures of the mandible are fully described. The treatment by wiring is discussed and excellent illustrations show how the lower jaw may be splinted against the upper teeth. The authors give their own methods of reducing displaced fractures by elastic (rubber band) traction attached either to the upper teeth or to a metal stay incorporated in a plaster head piece. Proper emphasis is placed upon mouth hygiene in the various methods of treatment.

The fractures of the maxilla and the zygoma are classified and appropriate treatment is described for each type. The chapter on Roentgenographic technique by Dr. Ennis clearly describes the approved methods of making Roentgen ray exposures for the individual types of fractures. Dr. Scogin gives an excellent chapter on the too-often-neglected dietary management of patients with fractures of the jaws.

The book is written so that he who runs may read. The text is profusely illustrated showing clearly the methods of treatment described in it. At the end of each chapter is a summary of the methods of treatment outlined according to the type of fracture. The monograph makes available to the general surgeon, the dentist and others who treat these fractures, the results of many years of experience in dealing with them. It is without doubt the most complete and useful book in its subject which has yet been printed.

L. F.

TEXT BOOK OF PHYSICAL THERAPY, VOL. I. By WILLIAM BENHAM SNOW. Pp. 708; 183 illustrations. New York: Scientific Authors' Publishing Company, 1931. Price, \$10.00.

A SCHOLARLY presentation of a book on physical therapy giving outlines of method and dosage is a well-known want. The present book is divided into a section of 20 chapters on the Constant and Static Current and the diseases to be treated with it; another section of 14 chapters on the physics, physiology and therapeutics of High Frequency Currents and a final section of 8 chapters on Electrosurgery. While the book undoubtedly contains much valuable material, it attempts so much not strictly in its domain that more pertinent material is often inadequately treated. It also seems as if too widespread claims were made for treatment of various conditions that are usually considered to be better handled in other ways.

E. K.

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HEALTH ON THE FARM AND IN THE VILLAGE. By C.-E. A. WINSLOW, DR. P.H., Professor of Public Health, Yale School of Medicine, Pp. 281; illustrated. New York: The Macmillan Company, 1931. Price, \$1.00.

THIS book is a review and an evaluation of a county health demonstration carried on with the coöperation of the Milbank Memorial Fund in Cattaraugus County, New York from 1923-1929. In addition the author considers the applicability of a similar complete public health program to other rural areas. The outstanding lesson, according to Dr. Winslow, is the "urgent importance, the great difficulty and the high cost of adequate health service for rural communities" (p. 16). To carry on such a program under reasonably comparable conditions would cost about \$2.50 per capita.

The detailed tables and the keen analysis probably make this statement the most thorough study not only of the experience in one county but of the problems involved in securing necessary health supervision for the rural population of the United States.

A. F.

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NOGUCHI. By GUS ECKSTEIN. Pp. 419; illustrated. New York: Harper & Bros., 1931. Price, \$5.00.

UNQUESTIONABLY one of the most picturesque figures among medical investigators of this century, Noguchi explored realms still too little mastered to permit any worth-while attempt at evaluation today. Perhaps this is the justification for the colorful way in which his present biographer has chosen to envisage his subject. Approach-

ing perilously near the prevalent fictional type of biography, which is bad at best but most pernicious if applied to scientists, the author has chosen to dramatize in jazzy style the man and the eccentricities of his startling career.

Born a peasant farmer's son in 1876, at the age of 3 Seisaku (who later changed his name to Hideyo on reading of a character named Seisaku who came to a bad end) so badly burned hands and feet that one hand remained permanently mutilated, though they were far from the stumps that the author alludes to (p. 53). The worst hand was later "reconstructed" by an enlightened provincial doctor—whence his stimulus to study medicine—and was an efficient aid to its owner's marvellous technical skill, as I can personally testify. Noguchi's financial difficulties in completing his medical studies, his ability to squander borrowed money, his chance encounter with Dr. Simon Flexner at Kitasato's Institute, which was later to bring him to Philadelphia first as assistant then as Demonstrator in Pathology at the University of Pennsylvania and to start him on Snake Venoms with Weir Mitchell, all are entertainingly and apparently accurately told. While Noguchi was in error in writing that "there is a rule not to employ foreigners" at the University, funds were scarce but were eventually procured through Dr. Mitchell. Within a year the Rockefeller Institute was organized with Flexner as its head, so Noguchi was sent on a Carnegie Fellowship to Madsen's Serum Institute at Copenhagen, before taking up his work at the new Institute which was to continue until his tragic death "in line of duty" in West Africa in 1928.

Noguchi's work on venoms stands firm and with his fertility in developing technical methods is sufficient to rank him one of the most influential bacteriologists of his day. Even though his work on trachoma and rabies, the globoid bodies of poliomyelitis, the cultivation of the *Spirocheta pallida*, and the spirochete that he thought was the cause of yellow fever still must await evaluation, his accepted contributions are more than sufficient to assure him lasting fame.

Of the man himself, Eckstein has given an inclusive, forcible and colorful picture. His tremendous energy when aroused, alternating with periods of "incredible laziness," his oriental artistry, his absorbing passion for research, his vivid love of life receive sympathetic and efficient handling by a friend who has given loving care to his work.

Noguchi's imaginative fancy runs through many passages quoted from his correspondence: "At that time I will be in the springtime of 27 or 28, with blood and spirit in vigor, and that is not too late to shake my arms around and to feel heaven and earth too small." . . . "I cannot speak yet concerning my final purposes and desires, but once I go abroad and succeed, I will speak again. If I speak before, it is forcing the bud unwillingly and there is no per-



fume, nothing. Therefore silence is the flower. Please be sure to cover this from those not concerned." "If it falls before it blooms what is the plum blossom?" "At my parting you showed me kindness like sea and mountain. . . . Colds are source of every disease, so I hope the master will take care of honorable wife. . . . Please remember me to all who have eaten out of the same kettle. With bent neck."

His reply to a request for biographical details is also illuminating. "Born, practiced dentistry, studied medicine, taught physiology, learned not much; read two or three men, learned a little; came to know two or three women, learned a good deal; made friends with two rats, learned prodigiously; wrote about the rats, continued to write." E. K.

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AN INTRODUCTION TO GYNECOLOGY. By C. JEFF MILLER, M.D. Professor of Gynecology, Tulane University School of Medicine. Pp. 327; 117 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, \$5.00.

As the title indicates, this book is merely supposed to be for the student who is beginning his course in gynecology and was written because the author was convinced that such students lack the ability to use the more extensive works selectively. Therapy is not discussed because the author believes that the treatment of disease is no concern of the junior student. The book well fills the gap between a simple outline and the usual textbook and is replete with present-day views on gynecology, especially in the sections devoted to physiology and internal secretions. The illustrations, although practically all taken from other standard books on the subject, are adequate for a treatise of this size except in the section on the development of the female genital organs. This subject, which is usually quite confusing to students, could be better elucidated by one or two carefully selected diagrammatic sketches. His students, for whom the book was compiled, can be thankful to him for the efficient manner in which he has selected the latest thoughts of the foremost gynecologists and incorporated them in such a small book. F. B.

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RECENT ADVANCES IN PULMONARY TUBERCULOSIS. By L. S. T. BURRELL, M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), Senior Physician to Royal Free Hospital. Pp. 240; 49 illustrations. Second Edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1931. Price, \$3.50.

In the preface to the first edition of this book the author says "Most of the book deals with treatment, and no attempt has been

made to describe physical signs or morbid anatomy, because the work is intended for practitioners and senior students and not as an examination textbook." In the preface to the second edition he says "The book is intended to bring to the notice of the practitioner and senior student the recent advances in our knowledge of tuberculosis and is not a treatise for the specialist."

With these limitations the book hardly lives up to its title for about two-thirds of the space is devoted to treatment, the other third being given to a mere statement of certain fundamental and well proven facts about tuberculosis in general. Also the word "Recent" must not be taken too literally as the new treatments discussed were first proposed 10 to 20 years ago, but after all this is in keeping with the general tempo of a disease the treatment of which is measured in years.

Pneumothorax is treated at some length but the other methods of treatment referred to are given only two or three pages at most. The most recent advance in the surgical treatment of pulmonary tuberculosis, namely phrenicectomy and thoracoplasty, are only referred to very briefly. In all this the author voices his own experience and quotes from his own cases to an extent that makes it impossible to consider this a broad cross section of general opinion on the subjects discussed.

R. E.

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## BOOKS RECEIVED.

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### NEW BOOKS.

*A System of Bacteriology in Relation to Medicine. Vol. 9. Technical Methods—General Index.* By various authors. Pp. 363; 86 illustrations. London: Medical Research Council, 1931. Price, £ 1.1.9 for this volume; for the set £ 8.14.9. Obtainable in the United States at British Library of Information, 5 E. 45th St., New York City.

*The Surgical Clinics of North America, Vol. 11, No. 5 (Pacific Coast Surgical Association Number, October, 1931).* Pp. 279; 109 illustrations. Philadelphia: W. B. Saunders Company, 1931.

*Tables of Food Values.* By ALICE V. BRADLEY, B.S., Supervisor and Instructor of Nutrition and Health Education, State Teachers College, Santa Barbara, Calif. Peoria, Illinois: The Manual Arts Press, 1931. Price, \$2.00.

*Simplified Diabetic Management.* By JOSEPH T. BEARDWOOD, JR., A.B., M.D., F.A.C.P., Chief of Diabetic Clinic and Associate Visiting Physician, Presbyterian Hospital in Philadelphia, and HERBERT T. KELLY, M.D., A.A.C.P., Associate in Diabetic Clinic, Presbyterian Hospital in Philadelphia. Pp. 191; 7 illustrations. Philadelphia: J. B. Lippincott Company, 1931. Price, \$1.50.

- Lezioni di Medicina Biologica.* By C. MARTELLI. Pp. 548; illustrated. Naples: Edizioni Rinascenza Medica, 1930.
- The Early History of Yellow Fever.* By HENRY ROSE CARTER, M.D., Assistant Surgeon-General (Retired) United States Public Health Service. Edited by LAURA ARMISTEAD CARTER and WADE HAMPTON FROST. Pp. 308; 5 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, \$5.00.
- Physicians' Manual of Birth Control.* By ANTOINETTE F. KONIKOW, M.D. Pp. 245; illustrated. New York: Buchholz Publishing Company, 1931. Price, \$4.00.
- The Child from One to Six. His Care and Training. Publication No. 30.* Pp. 150; illustrated. Washington: U. S. Department of Labor Children's Bureau, 1931.
- A useful, practical guide that should have wide distribution in American homes.
- Pathology, Bacteriology and Applied Immunology for Nurses.* By ROBERT A. KILDUFFE, A.B., A.M., M.D., F.A.S.C.P., Director Laboratories, Atlantic City Hospital. Pp. 324; 112 illustrations. Milwaukee: The Bruce Publishing Company, 1931. Price, \$2.50.
- A Text-book of Neuro-anatomy.* By ALBERT KUNTZ, PH.D., M.D., Professor of Micro-anatomy in St. Louis University School of Medicine. Pp. 359; 197 illustrations. Philadelphia: Lea & Febiger, 1931. Price, \$5.50.
- Medical Films and Their Sources.* By WILLIAM F. KRUSE. Chicago: Bell & Howell Company, 1931. Gratis.
- A survey of 538 reels of 16-mm. films on medico-surgical subjects with information as to how they may be obtained.
- The Foundations of Medical History.* By SIR D'ARCY POWER, K.B.E., F.R.C.S. (ENG.), Consulting Surgeon to St. Bartholomew's Hospital, Honorary Librarian of the Royal College of Surgeons, etc. With an Introductory Note by WILLIAM H. WELCH. Pp. 182; 3 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, \$3.00.
- The Medical Clinics of North America, Vol. 15, No. 2 (Philadelphia Number, September, 1931).* Pp. 303; 37 illustrations. Philadelphia: W. B. Saunders Company, 1931.
- Medical Administration of Teaching Hospitals.* By EMMET B. BAY, M.D. Pp. 136. Chicago: University of Chicago Press, 1931. Price, \$2.00.
- Nucleic Acids.* By P. A. LEVENE, The Rockefeller Institute for Medical Research, and LAWRENCE W. BASS, Mellon Institute of Industrial Research, now Assistant Director of Research, The Borden Company. Pp. 337; 14 figures. New York: The Chemical Catalog Company, Inc., 1931. Price, \$4.50.
- Annals of the Pickett-Thomson Research Laboratory, Vol. 7, July, 1931.* Pp. 441; 35 plates. Baltimore: The Williams & Wilkins Company, 1931. Price, \$10.00.
- Surgical Pathology of Prostatic Obstructions.* By ALEXANDER RANDALL, M.A., M.D., Professor of Urology, University of Pennsylvania. Pp. 267; illustrated. Baltimore: The Williams & Wilkins Company, 1931. Price, \$7.00.
- Recent Advances in Allergy.* By GEORGE W. BRAY, M.B., CH.M. (Sydney), Asthma Research Scholar, The Hospital for Sick Children, London. With Foreword by ARTHUR F. HURST, M.A., M.D. (OXON.), F.R.C.P., Senior Physician, Guy's Hospital; Chairman Medical Advisory Committee, Asthma Research Council of Great Britain. Pp. 432; 98 illustrations including 4 colored plates. Philadelphia: P. Blakiston's Son & Co., Inc., 1931. Price, \$3.50.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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AND

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**Infection in the Epidemiology of Undulant Fever in the General Population and in Selected Groups in Iowa.**—It has been observed that occasionally in individuals in whom there is no evidence of undulant fever there will be found positive agglutination reactions, although in the majority of instances there is a close relation between the clinical evidence of the disease and the positive agglutination. In borderline cases, however, it should be necessary to know, in order properly to interpret the results, the incidence of infection in the general population. JORDAN (*J. Infec. Dis.*, 1931, 48, 526) studied the results of agglutination tests on specimens of blood serum giving negative Wassermann reactions which would represent the general population. The sera of a group of people who had come in close contact with presumably infected cattle were also tested. These persons represented veterinarians, healthy employees of packing houses and a selected group who used raw contaminated milk. This latter group was selected because of the fact that it is very generally assumed that *Brucella* infection is transmitted through either direct contact with livestock or through the consumption of raw dairy products. In the present study there were used 1026 sera sent to the state laboratory for Wassermann tests. In this series there was no agglutination in approximately three-fourths of instances, but in about 25 per cent there was partial or complete agglutination in lower dilutions, while 0.3 per cent showed agglutination at 1 to 40 and 1 to 80. A questionnaire was sent to the physicians who sent these sera in asking for information regarding the people who showed partial or complete agglutination. One hundred seventy-six of these were answered. The great majority of these individuals had no contact with livestock, but it was found that contagious abortion of cattle was prevalent in 25 per cent of the cows in that community

and in 14 per cent infection was present in hogs. In only 3 instances was a past history given of an afebrile attack which might have been undulant fever. From these studies it is deduced that since nearly 8 per cent of the general population has no contact with livestock, presumably the use of raw dairy products accounts for their agglutinations for *Brucella*. A group of veterinarians was studied. One hundred and twenty sera were examined, 66 of which were negative and 54, or 45 per cent, showed partial or complete agglutination in dilutions of 1 to 5 to 1 to 40, 5 per cent showing partial or complete agglutination in the last dilution. As the veterinarians definitely showed a higher agglutination ratio than the general population, it was assumed that this is due to the greater contact with cattle. With the workers in packing houses the figures were even more striking. Of 220 sera 152 were negative, whereas the remainder showed a relatively high agglutination titer, 14 per cent showed a complete agglutination in 1 to 80 to 1 to 1280. In this group 14 gave a definitely suggested history of undulant fever. In a group of individuals that were using a milk supply that was known to be contaminated, 70 per cent showed no agglutination and the remainder partial or complete agglutination in titers from 1 to 5 to 1 to 640. Infection with *Brucella melitensis* under any circumstance seems to depend upon the amount of raw dairy products consumed, the ratio of exposure and the number of organisms ingested. In addition to the deductions already drawn, Jordan raises the question as to whether or not natural immunity may not be a factor, particularly in children, which might explain a large number of reactions which showed "no agglutination."

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## SURGERY

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UNDER THE CHARGE OF  
T. TURNER THOMAS, M.D.,  
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**Tumors of the Extrahepatic Bile Ducts.**—SHAPIRO and LEFVEN-DAHL (*Ann. Surg.*, 1931, 94, 61) say that a clinical and pathologic study is presented of 15 cases of tumor of the extrahepatic bile ducts. These included 1 amputation neuroma of the cystic duct, 1 solid adenoma, 1 congenital cyst and 12 carcinomas. According to this material carcinoma of the extrahepatic bile ducts was twice as frequent as carcinoma of the gall bladder and three times as common as carcinoma of the head of the pancreas. It should be given, therefore, greater consideration in the differential diagnosis of lesions of the porta hepatis. The clinical course, especially that part of it which was severe enough to demand medical treatment was brief. The clinical syndrome was usually a typical jaundice and was usually not the first symptom. It was usually not painless and it was not always steadily progressive. The clinical picture was often masked by symptoms arising from accidental complications, particularly duodenal ulcerations or from metastases. The tendency of these tumors to colloid degeneration with

numerous goblet cells is an expression of the original intestinal character of the bile-duct epithelium. The frequency of duodenal complications is noteworthy. Metastases were common, extensive and widespread and in some cases dominated the clinical and pathologic picture. Small as they are, contrary to eurrent conception, these tumors send out metastases long before they announce their own presence. This may account for the present ungratifying permanent results of radical resection.

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**The Treatment of Lung Abscess and Empyema by Packing.**—CONNORS (*Ann. Surg.*, 1931, 94, 38) state that the pleural cavity is cleaned within 24 hours and remains grossly clean until the cure is effected. By the old method change of dressings daily or twice daily was necessary or else extensive apparatuses were employed. Even with the simple procedures close attention to details was necessary. By this method dressings are changed at comparatively infrequent intervals and may be forgotten for several days. The introduction of tubes is unnecessary and therefore a source of pleural irritation is removed. It is well known that drainage will continue as long as a tube is allowed to remain in a sinus. It is also noteworthy that no cases of osteomyelitis of the rib developed in the cases since there was no tube to rub for days against a rib adjacent to a thoracotomy wound. It prevents the discomfort which may be due to a mobile mediastinum by fixing it. In several cases when the tight packing was removed discomfort was experienced which was relieved by the reinsertion of the packing. The large thoracotomy wound with the help of the Cameron light permits of a perfect inspection of the pleural cavity and allows the operator to remove all fibrin and break up the necessary adhesions and pockets. And not least interesting it has allowed a clear view of the mechanism of the cure of the empyema cavity and has helped improve the methods directed toward cure.

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**Collateral Respiration in the Lung.**—ALLEN and LINDSKOG (*Surg., Gynec. and Obst.*, 1931, 53, 16) declare that the branches of the bronchial tree in a single lobe of the lung intercommunicate at the periphery in such a manner as to permit the transfer from one to another of gases, fluids and particulate matter. The process of transfer is referable both to diffusion and to passage through minute openings, but this point requires further investigation. The airways of two neighboring lobes do not so communicate. This bears economic significance to respiratory function after bronchial obstruction; for a lobule of lung with centrally obstructed bronchus may yet breathe satisfactorily by using the peripheral interconnections with adjacent free lobules. This function is termed collateral respiration. Collateral respiration plays two economic rôles in the lobular form of bronchial obstruction, namely, that of preventing the development of atelectasis and that of rendering important assistance to the bronchoeliminative forces. Collateral respiration may be excluded by closure of those airways along the margins of the obstructed lobule, which have to do with the intercommunication. This may result from blockage with secretions or

other materials or from shutdown during periods of shallow breathing. The latter circumstance is probably a factor in the pathogenesis of postoperative atelectasis.

**Carcinoma of the Breast in the Young.**—LEE (*Arch. Surg.*, 1931, 23, 85) claims that cancer of the breast in young women is a much more menacing disease than it is in mid-life or in old age. The course is often dramatic in its rapidity, almost simulating an infectious process. When the first symptom is a diffuse enlargement of the breast, a redness overlying the mammary gland or pain, surgical intervention is futile. A more careful examination of younger as compared to older women must be exercised before radical operation is undertaken. Early recurrence is more frequent in younger than in older women and indicates either a poorly chosen case for surgical intervention or poor surgical technique or both. In many of these patients reliance must be placed entirely on radiation therapy. In well-chosen cases well-planned adequate irradiation combined with carefully performed radical amputation yields the best results.

## THERAPEUTICS

UNDER THE CHARGE OF  
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**For and Against the Nirvanol Treatment of Chorea Minor.** GOEBEL (*Deutsch. Med. Wchnschr.*, 1931, 57, 1313) presents a clear discussion of the advantages and disadvantages connected with the treatment of chorea minor by nirvanol (phenylaethylhydantoin). He points out from his own experience and that of a number of others that the appropriate administration of this drug yields better results in the treatment of chorea than are given by any other means yet employed. Its administration not only controls the symptoms of chorea but there is strong evidence to show that it greatly diminishes the frequency of the development of endocarditis. The most satisfactory plan of treatment is the administration of large daily doses of nirvanol, which are to be continued up to the beginning of so-called nirvanol sickness but in no event for longer than 12 days. Against the striking therapeutic value of nirvanol are, however, a number of serious objections. Among these there is the fact that the drug must be pushed to the point of developing moderately severe intoxication manifested by skin eruption, high temperature and a pronounced leukopenia. In the majority of cases cessation of administration is followed within a comparatively few days by subsidence of these manifestations, but in some they are certain to progress and in others, after subsidence of the symptoms, their recurrence may take place spontaneously. There is conclusive

evidence that the leukopenia is due to a definite depression of bone-marrow function. Along with the other symptoms mentioned there are also anginal manifestations in the throat, stupor, muscular cramps, cyanosis and frequently inflammation of the submaxillary glands. Definite instances of nephritis are furthermore encountered as a result of the actions of nirvanol and in several instances these have lead to death of the patient. The author concludes that, although nirvanol has proved to be a most valuable therapeutic agent in chorea minor, its administration is associated with such severe manifestations of discomfort and even with such risks of serious or fatal intoxication that its use cannot be recommended except in severe cases and then only after all other remedies have failed.

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**The Effect of Roentgen Rays in the Treatment of Bronchial Asthma, Eczema and Hay Fever.**—The reports of the effect of Roentgen rays on certain allergic conditions is based mainly on animal experiments and scattered case reports. SCHREW and WILLMS (*München. Med. Wchschr.*, 1931, 20, 832) confirm, on the basis of their observations on patients, the beneficial effect of Roentgen rays on bronchial asthma, eczema and hay fever. Of the 9 cases with hay fever treated 6 were "cured," 1 improved and 2 remained unchanged. The authors claim that the therapeutic effects were not due to psychic influence. The nose and the mediastinum were the areas exposed to Roentgen rays in these patients. Of the 14 cases with bronchial asthma receiving treatment over the mediastinum, 8 were cured, 4 showed improvement, and 2 remained unchanged. Of 14 cases with eczema and evidence of cutaneous hypersensitivity following Roentgen ray treatment, 9 showed a diminished cutaneous reaction, in 4 the reaction was unaltered and in 1 it was more intense. The authors claim that in these conditions the Roentgen rays produce a desensitization.

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## PEDIATRICS

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UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
OF PHILADELPHIA.

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**Pertussis.**—MAGEE (*J. Am. Med. Assn.*, 1931, 97, 922) feels that rectal ether is the treatment of choice for pertussis in view of the consistently good results obtained with it and the ease of its administration. When ether was used alone or in conjunction with other methods such as vaccines and ephedrin it gave rise to a greater reduction in leukocytes per day than the other commonly used methods. As a preventive measure, rectal ether was of no value in 10 cases in which it was used for prophylaxis. The constant bathing of the respiratory mucous membrane with a weak solution of ether probably accounts for its favorable results. Rectal ether greatly ameliorates the severity of pertussis and shortens its course, especially when begun in the paroxysmal stage. Its influence is greater among children over 1 year of age.



White and differential blood counts and isolation of the Bordet-Gengou bacillus give two reliable aids in arriving at an early diagnosis of pertussis. The latter method furnishes a means of enforcing a scientific quarantine and is a means of reducing the incidence of the disease. While rectal ether is not considered a specific for pertussis and while it may add little to the armamentarium for that disease, its simplicity and its effectiveness from the standpoint of symptomatic relief justify its use until a better form of treatment is found and proved superior.

**Cod-liver Oil Emulsified in an Extract of Germinating Grains: Its Tolerance by the Infant Gastrointestinal Tract and Its Prophylactic Value.**—JARVIS (*Arch. Ped.*, 1931, 48, 502) found that deficiency disease prophylaxis became more efficient when vitamin sources are combined in a mixture of such tolerance to the infant's gastrointestinal tract as to permit its early and continued routine use during the early months of life, during which time hesitancy is usually encountered in undertaking such a procedure with the more common diversified sources of such administration. An emulsion of cod-liver oil in a concentrated extract of the germinating grains of wheat, oats and malted barley was found to be exceptionally well tolerated by the infant's gastrointestinal tract. This emulsion contained vitamins A, B and D but lacks vitamin C, which should be added by adequate doses of orange and tomato juice. Although containing 30 per cent by volume of cod-liver oil, this mixture yields a vitamin D potency equal to that of the pure cod-liver oil. This is probably due to the greater availability in assimilation due to the complete emulsification by the gastrointestinal tract and also possibly due to a coördinating activity of the A and the B factors.

**The Early Diagnosis of Rheumatic Heart Disease in Children.**—SEHAM, SHAPIRO, and HILBERT (*Am. J. Dis. Child.*, 1931, 42, 503) states that in 809 patients admitted during a period of 7 years, 46 per cent of the cases were diagnosed as organic heart disease and 54 per cent as "no heart disease." Of 379 cases of organic heart disease, 18 per cent were congenital lesions of the heart, 74 per cent were rheumatic in origin, 3.6 per cent were due to other causes and 4.4 per cent were undiagnosed. For early diagnosis of heart disease of rheumatic origin all available methods were necessary. The problem of differential diagnosis revolves around chiefly the children who present the following symptoms: systolic murmur, with or without circulatory signs or symptoms; rheumatism and a systolic murmur that has escaped carditis; rheumatism and a systolic murmur that ultimately develops into chronic endocarditis; and congenital heart disease, especially patency. According to the statistics of this study, the most reliable means of diagnosis was history. A questionnaire was found to be more effective than informal questioning. Rheumatism alone caused 39.3 per cent of rheumatic heart disease. Rheumatism in combination with other causes was responsible for 83.1 per cent. Growing pains alone accounted for 2.3 per cent. The roentgenogram taken at a distance of 6 feet was found to be as reliable method for the practical purpose of diagnosis as the orthodiagram. The 50 per cent cardiothoracic index that is used as normal standard was found to be statistically not reliable. In 66 per

cent of normal children the cardiothoracic index is between 44 and 50 per cent, and the remaining 33 per cent fall between 41 and 51 per cent. In 25 of 100 consecutive examinations of normal children, one is likely to find a cardiothoracic index of over 50 per cent. A positive esophogram reveals a dilatation of the left auricle. This does not appear in children with congenital heart disease, in those with miscellaneous heart disease or in normal children. The esophographic results were positive in 55 per cent in cases diagnosed as mitral regurgitation. In this group the esophogram is more sensitive than auscultation. It gives positive observation in 67 per cent in the group diagnosed as double mitral disease and 77 per cent in those double mitral disease and aortic regurgitation. The so-called functional tests are of no value in determining the myocardial sufficiency of the heart.

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## DERMATOLOGY AND SYPHILIS

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UNDER THE CHARGE OF

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**An Appraisal of the Newest Arsphenamin Synthetic, Bismarsen, in the Treatment for Syphilis, Based on 7666 Injections in 341 Cases During 5 Years.**—STOKES, MILLER and BEERMAN (*Arch. Dermat. and Syph.*, 1931, 23, 624) summarize a 5-year study of bismarsen. Some of their most important conclusions are as follows: (1) Local reaction to intramuscular injection (the only route) occurs following 2 per cent of injections as stiffness and moderate pain, most marked on the second or third day. It is largely controllable by prolonged massage, good technique and hot applications. (2) Systemic reactions occur following 0.5 per cent of injections, or in 11 per cent of patients, and include nitritoid crises, mild gastrointestinal reactions and cutaneous reactions. (3) The incidence of primary exfoliative dermatitis is 1 case in 5500 injections—about that of neoarsphenamin and less than that of other arsphenamins. (4) Three cases of jaundice have thus far been reported and no cerebral accidents. (5) Herxheimer effects are comparatively insignificant or absent. (6) The effect on the Wassermann reaction in early syphilis is excellent and lasting. (7) The proportion of all forms of relapse was 12 per cent in early syphilis as compared with from 20 to 40 per cent in a carefully studied series treated with other drugs and modern systems. (8) Intermittent is less effective than continuous treatment with the drug. Two injections a week of 0.2 gm. are preferable in early syphilis to a total of 40 to 60 treatments, usually followed by bismuth. (9) The greatest promise for bismarsen is in early syphilis. In cutaneous, mucosal and osseous gumma bismarsen is slower than other arsphenamins and is not recommended. In prenatal syphilis

the action of the drug, while not fully appraised, seems disappointing. It is not advisable in cases of interstitial keratitis because of its slowness of action. (10) Bismarsen is a safe and effective drug in the treatment of patients with the aortic types of vascular syphilis. The initial dose in such cases should not exceed 0.05 gm. (11) 50 per cent of patients with nonparetic types of neurosyphilis had blood and spinal fluid reduced to normal by mixed forms of standard treatment, preponderantly bismarsen. There was relatively little influence noted on the paretic formula in the spinal fluid. (12) Fair to good symptomatic improvement occurred in meningeal headache and lightning pains in tabes.

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**Erythema Infectiosum.**—LAWTON and SMITH (*Arch. Int. Med.*, 1931, 42, 28) report an epidemic of 97 cases of erythema infectiosum occurring in Granford, Conn. The epidemic was similar in all respects to previously reported outbreaks. Erythema infectiosum seems to be a distinct clinical entity and all evidence points to its being transmitted from person to person, although the mode of transmission and the etiology of the disease are unknown. Experimental work is cited, all of which is negative. Clinically the characteristic features are the rash, its distribution, the evanescence, the relatively long duration and the absence of symptoms. There is usually no leukocytosis but a tendency toward eosinophilia and a relative lymphocytosis.

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## GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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AND

FRANK B. BLOCK, M.D.,

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**Cancer of the Cervix.**—Clinically, DEEVER (*Ann. Surg.*, 1931, 94, 381) divides cancer of the cervix into three groups: the operable, questionably operable and the inoperable. The operable group includes those where the cervix is hard and nodular, perhaps enlarged, and where the tissues are friable, but there is as yet no ulceration or evidence of metastasis. He considers these the most favorable cases for complete hysterectomy with removal of the glands with the expectation of a very low mortality. Where there is ulceration of the cervix with exuberant granulations which bleed freely to the slightest touch and there is no palpatory infiltration in the broad ligaments he uses radium and later performs complete hysterectomy. Such cases are considered questionably operable but he believes they present a fairly good temporary outlook. Sooner or later, however, most of them return with involvement of the broad ligaments and then deep Roentgen ray treatment is given but usually with little benefit. Where the entire vaginal cervix is

diseased he advises radium and deep Roentgen ray therapy and although they improve locally, eventually all die of the disease. A survey of the end results of 140 cases treated in the Lankenau Clinic shows that the expectancy of life is somewhat better after operation than after irradiation alone. The mortality of the entire group was 57.8 per cent. Eighty-three received radium only with a mortality of 70 per cent; 18 were treated by operation and radium with a mortality of 55 per cent, while the 39 treated by operation alone showed a mortality of 33.3 per cent. On the other hand, in view of the fact that many cases are hopeless when first seen, radium treatment is less distressing than operation and provides temporary improvement and he believes that radium is also of value in bringing some cases to a state of operability. Nevertheless, he is not very enthusiastic about irradiation. He has never seen an adenocarcinoma cured by this means and in the cases that have advanced to the stage of infiltration of the broad ligaments he has never seen dissipation of the infiltrate although pain has sometimes been relieved. In view of the fact that in about 40 per cent of the cases the regional glands are already cancerous when the patients come for treatment and that the radiologist cannot tell beforehand whether or not the glands are involved, he may treat cases in which radium is useless and thus deprive them of the benefits of surgery which the author believes may effect a cure in about 25 per cent of cases with glandular involvement. Therefore, he believes that the time has not yet arrived to discard surgery in the treatment of cancer of the cervix but rather give the operable cases the advantages of surgery and allow the inoperable ones the consolation of irradiation. While the opinion of such a preëminent surgeon as Deaver is entitled to careful consideration, it should be remembered that it is at variance with the teachings of most of the larger clinics where the radical operation for cervical cancer remains only as a memory of historical interest.

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## OPHTHALMOLOGY

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**The Eye in Diabetes.**—According to ASCHER (*Klin. Wchnschr.*, 1931, 10, 1407) normally the sugar content of the aqueous is somewhat lower than that of the blood. In diabetes, the sugar content rises; but variations, either rise or fall, do not occur as rapidly as in the blood. The aqueous becomes relatively acid, loses some of its buffer substances and contains considerable acetone. These chemical changes are appar-

ently responsible for the degeneration of the posterior surface of the iris, for the variations in refraction of the lens, and for the development of diabetic cataract. Characteristic of diabetes is the edematous swelling of the pigment epithelium of the iris as a result of which pigment is set free into the aqueous in the course of intraocular operations. Rubeosis iridis, noninflammatory new vessel formation in the sphincter portion of the iris, is also characteristic of diabetes. This always leads to glaucoma. Two forms of iritis also occur, one metastatic from suppurations elsewhere in the body and another probably dependent on metabolic changes. Atropin is sometimes ineffective in the treatment of diabetic iritis, particularly during the use of insulin. Changes in pupillary reactions are very rare in diabetes; disturbances of accommodation are more frequent, due either to weakness of the ciliary muscle or to changes in the lens substance. Changes in refraction in diabetes are usually in the direction of increased myopia in the early cases and of increased hyperopia in the cases under treatment with falling blood sugar. They are due to variations in the refractive index of the lens which are most probably associated with the changing relations in concentration between the blood and the aqueous on the one hand and the lens on the other. Myopic changes in the diabetic eye may be a forerunner of cataract formation. In diabetics over 40 years the change may be a slow one, due to increasing sclerosis of the lens as in ordinary senile cataract. In younger diabetics the typical rapid cataract formation takes place as the result of increase of fluid in the cortical layers of the lens. Beginning change of this second type may remain stationary or regress under insulin therapy. They appear only in the presence of high blood sugar and acidosis. If care is taken to eliminate bacterial infection of the conjunctiva and to lower the blood sugar and rid the patient of acidosis, cataract extraction can be performed in diabetics without added risk. Intracapsular extraction is preferable. Lipemia retinalis is a rare but typical finding. The fat content of the blood varies usually between 4 per cent and 8 per cent, and acidosis is always present. It affects only the retinal, not the choroidal vessels. Retinitis is rare in diabetics under 40. It is still questionable whether vascular changes are necessary for the development of the retinitis. The central punctate retinitis of Hirschberg seems to occur at times in uncomplicated diabetes. The hemorrhagic forms are apparently always associated with high blood pressure, vessel changes and kidney damage. The basis of the retinal disease seems to be in vascular spasms which lead to disturbances of nutrition and the deposit of lipoids and fibrin. Histologically, marked changes are found in the capillaries and veins, hyaline degeneration of the walls with sclerosis and partial thromboses. In rare cases, hemorrhages take place into the vitreous with resultant retinitis proliferans. According to Onfray, about 50 per cent of patients with diabetic retinitis die within 3 years. The prognosis does not depend so much on the diabetes, however, as on the height of the blood pressure and the amount of kidney damage. In the presence of marked vessel changes insulin therapy should be used with caution. The soft eyeball which is characteristic of diabetic coma may develop before the onset of unconsciousness and may be a warning of the danger of coma. The intraocular hypotension is probably dependent on loss of fluid, especially from the vitreous rather than directly on the loss of alkali reserve from

the blood and aqueous. This view is supported by the finding of low intraocular tension in insulin hypoglycemia. Retrobulbar neuritis occurs in diabetics probably from the effect of misuse of alcohol and tobacco on an optic nerve sensitized by circulating toxic products of diabetic metabolism. It occurs more frequently in men usually over the age of 50 and is characterized by a macular scotoma, especially for blue. In the treatment, withdrawal of tobacco and alcohol is necessary, as well as careful diet and insulin therapy. The disturbances of adaptation which occur frequently in diabetics may be explained on the basis of chemical changes in the pigment epithelium and in the sensory cells of the retina. Ocular muscle paralysis, affecting sometimes the third nerve but more usually the sixth, and hemianopsias are to be ascribed to accompanying high blood pressure and vascular disease rather than to the diabetes proper.

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## RADIOLOGY

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**Treatment of Osteogenic Sarcoma by Means of Irradiation.**—After study of 58 cases of osteogenic sarcoma treated by irradiation, and after reviewing similar work in other clinics, PFAHLER and PARRY (*Am. J. Roentgen. and Rad. Therap.*, 1931, 25, 761) feel justified in concluding that the only two methods of treatment for this disease are irradiation or surgery or the two combined. The results from irradiation are at least equal to, and the authors believe, better than, those obtained by surgery. Preliminary irradiation of the tumor area and irradiation of the chest followed by amputation has given best results to the authors. A biopsy for diagnosis is desirable, but should be preceded by deep Roentgen therapy for a month.

**Osteitis Fibrosa Cystica Generalisata With Hyperparathyroidism.**—It is becoming known that hyperparathyroidism from tumor or other lesions of the parathyroids may give rise to absorption of lime salts from the bones. DRESSER and HAMPTON (*Am. J. Roentgen. and Rad. Therap.*, 1931, 25, 739) report 2 cases and regard the condition as a form of osteitis fibrosa cystica, and consider the Roentgen picture to be characteristic. The disease affects not only the bones of the extremities but also the skull, spine, ribs and pelvis. It is seen more often in women than in men and occurs most commonly between the ages of 30 and 60 years. Pain, muscular weakness and postural abnormalities are common symptoms. Medical advice is often sought because of a spontaneous fracture. Roentgenologic changes in the affected bones are striking. In the skull, the bones of the vault present a generalized finely mottled,

granular texture, produced by closely spaced areas of diminished density which are irregular in outline and vary from a fraction of a millimeter to a centimeter or more in diameter. A similar appearance may be seen in the vertebral bodies, Often the most extensive changes are observed in the pelvis, the bones of which may show an extreme degree of decalcification with replacement of the normal bone structure by large trabeculated cystic areas. There is generalized decalcification of the ribs and occasional cystic areas associated with expansion and thinning of the cortex. The long bones present well-defined cysts which are frequently trabeculated and which may be situated anywhere in the diaphysis. In addition to the cystic areas there is generalized decalcification of the long bones with corresponding loss of density and thinning of the cortex.

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## NEUROLOGY AND PSYCHIATRY

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---

**Hemorrhage of the Brain.**—BOWMAN (*Arch. Neurol. and Psychiat.*, 1931, 25, 2) presents his investigations of hemorrhage of the brain based on cases of apoplexy in older and younger persons and on cases of gunshot wounds in which the patients lived for several hours. The major portion of his paper discusses rather well the various concepts of hemorrhage of the brain. He presents these ideas lucidly and briefly and concludes his discussion of their findings by presenting his own personal observations. In his studies he found large hemorrhages from the rupture of large vessels the rule. "There," he stated, "a disharmony existed between the blood pressure in the vessel at the moment of rupture on the one side and a weakness of the vessel wall on the other." In the cases in which weakness of the vessel wall plays the chief part, he pointed out that the ruptured vessel would generally not be the only one with a weakness of the wall, but in the adjacent area other vessels with the same alteration of the wall would be found. Normal as well as altered vessels found in the area of a hemorrhage were found ruptured. When no alteration of the vessel wall could be demonstrated, he stated that one must consider the possibility of the blood mass, which forces its way and pushes everything aside. "The blood coming from these small normal vessels and that which flows out of the degenerated vessels will greatly increase the quantity of the extravasated blood. . . . If the hemorrhage lasts longer, several factors have an influence. There may be ischemia and chemical action from the changed tissue or from the extravasated blood. Tissue reaction develops especially along the vessels; a perivascular tissue-cell infiltration arises." In comparing other observations in several cases of apoplexy with those made in a study of gunshot wounds, the author found that

there were curious analogies between them. In a relatively short time, vessel walls with necrosis are visible in the circular space of the destruction by a gunshot wound. He found it striking that the neerobiotic process of the vessel wall was progressing from the outside to the inside—it had also begun in a tissue that according to its connective-tissue structure ought to have more resistance. Therefore, he pointed out, one must think of chemical influences of the surroundings. He found that it could be demonstrated that there was blood inside and outside the meso-ectoderm membrane, that the blood corpuscles were lying in the perivascular space of Virehow-Robin and there was transportation of blood through the glial spaces of Held. Near the gunshot wound he noticed that there was also necrosis of vessels in consequence of influences originating in the surroundings. The extravasated blood propagated through the perivascular spaces of Virehow-Robin and through the glia spaces of Held. "Thus, in both apoplexia cerebri and gunshot wounds there are mechanical and chemical influences that are of great importance." In cases of a circular hemorrhage and of poli-encephalitis hemorrhagica superior there also was found a necrobiotic process of the small vessels, dependent on mechanical and chemical influences. In "red softening," tissue-cell infiltration was found, with degeneration and alteration of the vessels; this could be demonstrated in both recent and old hemorrhages. "Besides," he states, "in red softening the wall of the hemorrhage consists of three distinct layers from inside to outside: (1) brain tissue with extravasated material; (2) new-formed vessels with glia and lymphocytic elements, and (3) gliosis." He concludes his paper with the remarks, "It is not uncommon to make the clinical diagnosis of a cerebral hemorrhage and then to have the pathologist find no gross lesion at autopsy. Such cases used to be spoken of as 'hemiplegia without anatomic observations.' It is possible to explain, on a basis of transitory anemia, the various evanescent hemiplegias, monoparesis and aphasias . . .; total recovery may take place in one case, and in another that appears no worse at the beginning the neurologic signs may become permanent disabilities. In the first case there is evidently only a passing cerebral anemia, not prolonged enough to cause tissue destruction, and in the second there is actual tissue destruction of the cerebrum . . . The problem of cerebral hemorrhage is still new and challenging to investigators."

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## PATHOLOGY AND BACTERIOLOGY

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**Iodin Deficiency and Goiter.**—Most American scientists accept the theory that iodine deficiency is the cause of endemic goiter. Tanabe, in Germany, claims to have produced hyperplasia of the thyroid gland



by giving white rats a diet poor in iodine. HELLVIG (*Arch. Path.*, 1931, 11, 709) was unable to confirm the findings of Tanabe; attempts to produce goiter in white rats by feeding a diet poor in iodine gave only negative results. His observations, on the contrary, showed that a diet poor in iodine produced atrophy of the thyroid gland. Giving a diet rich in calcium and free from iodine produced a marked epithelial hyperplasia of the thyroid gland. A diet rich in calcium and iodine produced small colloid goiters. Thus, he showed that an excess of iodine in the diet exerts an inhibitory action on hyperplasia of the thyroid gland, in spite of a high content of calcium. Thus, the author concluded that an insufficiency of iodine in the food was neither the only nor the essential cause of endemic goiter. From the positive results obtained with a diet rich in calcium, it would appear that a positive agent is responsible for the development of goiter. This positive agent may not be a single specific factor, and this or these positive agents may not alone cause hypertrophy of the thyroid gland in the presence of a high amount of iodine in the food, nor may insufficiency of iodine in itself cause endemic goiter in the absence of the other agents that cause goiter, but when both are present the conditions for the development of hyperplastic goiter would seem to be at their optimum.

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**The Occurrence of Intranuclear Inclusions in the Nerve Cells in Poliomyelitis.**—Small intranuclear acidophilic inclusions in the nerve cells of experimental poliomyelitis, and in one human case were described by HURST (*J. Path. and Bacteriol.*, 1931, 34, 331). Fixation of the tissues in sublimate formol or Zenker formol, with subsequent coloration by Mallory's phloxin methylene blue, was found most suitable. In poliomyelitic cords some of the anterior horn cells may be seen in a stage of degeneration characterized by a complete loss of Nissl substance, irregularity of the cell outline and often extensive vacuolation of the cytoplasm. The nucleus is enlarged and mulberry shaped, and the nucleus may appear almost or wholly devoid of any acidophilic coagulum. In such cells the author was able to find inclusion bodies most readily. In serial section the bodies were nearly always multiple; they varied in size from fine granules to rounded structures, 4 to 5  $\mu$  in diameter, appearing bright red or bluish-pink. Often a large pinkish body had small red granules adhering to its surface. The outline of the bodies was sharper than that of the nodal masses of normal acidophilic material and frequently they were separated by a clear halo from remnants of normal nuclear material. The bodies occurred in the large anterior horn cells and less often in the smaller nerve cells of the anterior and posterior horns. In addition, the nerve cells of the brain stem and the Betz cells of the motor cortex were at times affected. The bodies always occurred in damaged cells but were never seen in completely necrotic cells. The bodies were most numerous during the first three days of paralysis. The bodies were never found during the incubation period and were difficult to find late in the disease.

## HYGIENE AND PUBLIC HEALTH

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**Food Poisoning: Attempts to Immunize Human Volunteers with Staphylococcus Filtrates That Are Toxic to Man When Swallowed.**—DACK, JORDAN and WOOLPERT have shown that broth filtrates prepared from certain strains of staphylococci produce symptoms of "food poisoning" (vomiting, diarrhea, weakness) when swallowed by man. Since the lower animals, including monkeys, are not visibly affected when fed with these filtrates any attempt to discover whether immunity to this toxic action can be produced is necessarily limited by the availability of human volunteers. A second attack of diarrhea can be produced in the same individual by feeding the same amount of filtrate after a week's interval. The present paper (*J. Prevent. Med.*, 1931, 5, 151) deals with the effects observed in 5 volunteers fed with gradually increasing doses of staphylococcal filtrates of known gastrointestinal toxicity. The doses of filtrates were administered in half pints of pasteurized milk. Four human subjects fed with gradually increasing doses of staphylococcus filtrates, reaching amounts of from 25 to 32 cc., appeared to develop some tolerance to the poison of the particular strain used in the immunization treatment. Heterologous filtrates (10 cc.) taken at the conclusion of the "immunizing" treatment produced no symptoms in one subject. Two other volunteers, however, when fed respectively 2 and 10 cc. of the filtrate of a heterologous strain, developed definite symptoms, which in the person receiving the larger dose were very violent. A fifth subject was extremely sensitive to small doses of filtrate and did not develop any tolerance. Rabbits injected intravenously with gradually increasing doses of staphylococcus filtrates developed a tolerance to the staphylococcus poison, both to that of the strain used in immunization and to that of a heterologous strain. Serum from four normal persons, from a patient with active chronic osteomyelitis and from one with an old healed lesion of osteomyelitis, when injected along with staphylococcus filtrate, did not protect rabbits against the staphylococcus poison. Serum from "immunized" men and rabbits did not protect monkeys or rabbits when it was mixed with potent filtrates and injected intravenously; nor did such serum protect a human volunteer who swallowed it mixed with a potent filtrate.

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**An Infection of the Rocky Mountain Spotted Fever Type.**—*Identification in the Eastern Part of the United States.*—BADGER, DYER and RUMREICH (*Public Health Reports*, 1931, 46, 463) in studies on the

typhus-Rocky Mountain spotted fever group of eruptive diseases, isolated from human cases a virus very similar to that obtained from the Rocky Mountain spotted fever cases as they occur in the western states. Tests on guinea pigs, monkeys and rabbits were all successful in producing an infection of the nature mentioned. Finally cross-immunity tests were performed with a virus derived from the western Rocky Mountain spotted fever region and with the virus of typhus fever. These cross-immunity tests indicated that the new virus was not to be differentiated from the Rocky Mountain spotted fever virus and was not related to the typhus virus at least insofar as such tests may make differentiation possible.

## PHYSIOLOGY

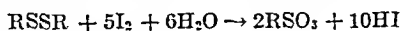
### PROCEEDINGS OF

### THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 19, 1931

**The Oxidation of Cystin by Iodin: A Consideration of Its Mechanism and of the Oxidation Reduction Potential of Thiol.**—K. SHINOHARA (from the Research Institute of the Lankenau Hospital, Philadelphia). The Okuda method<sup>1</sup> for the determination of cystin was studied because of the ambiguous end point and the excessive consumption of iodine when the titration is conducted in low concentrations of HCl (less than 2 per cent HCl). This excessive consumption of iodine has been explained by Bierich and Kalle<sup>2</sup> as due to partial oxidation of cysteine to cysteic acid instead of to cystin. Since bromine can effect the oxidation of disulphides to sulphonic acids, it might be expected that free iodine would do likewise. Hence the reaction between free iodine and cystine at low acidities was studied.

Investigation of the speed of the above reaction and its final equilibrium point supported the assumption that cysteic acid could be formed according to the reaction:



The cysteic acid was isolated and identified. A small amount of sulphuric acid was also formed.

Examination of the speed of the reaction indicated that it is probably made up of a consecutive series of bimolecular reactions. For this reason a number of hypothetical intermediate steps are proposed. Because of their instability these intermediate products have not been isolated.

The above results correspond to what would be expected from the studies of Dixon and Quastel<sup>3</sup> and Michaelis and Flexner<sup>4</sup> on the oxida-

<sup>1</sup> Okuda, Y. J.: Chem. Soc. Japan, 1924, 45, 1; Chem. Abstr., 1924, 18, 3400.

<sup>2</sup> Bierich, R., and Kalle, K.: Zeitschr. f. phys. Chem., 1928, 175, 11.

<sup>3</sup> Dixon, M., and Quastel, J. H.: J. Chem. Soc., 1923, 123, 2943.

<sup>4</sup> Michaelis, L., and Flexner, L. B.: J. Biol. Chem., 1928, 79, 689.

tion reduction potential of the system RSSR—RSH and support the conclusion that the disulphid form is not directly in equilibrium with sulphhydryl.

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**The Movement of Fluid Through the Human Capillary Wall in Relation to Venous Pressure and to the Colloid Osmotic Pressure of the Blood.**—EUGENE M. LANDIS (from the Robinette Foundation, University of Pennsylvania). Microinjection studies in man have shown that normal average capillary blood pressure is approximately equal to the colloid osmotic pressure of the blood. If the Starling hypothesis can be applied to fluid balance in man a relatively slight grade of venous congestion should cause the accumulation of fluid in the tissue spaces. Moreover, a rise in the colloid osmotic pressure of the blood should be accompanied by a reduction in the rate at which fluid accumulates with any given degree of venous congestion. These two points were tested by using a "pressure plethysmograph" to measure the rate at which fluid accumulated in the tissue spaces of the arm during venous congestion. Errors due to vasomotor variation were avoided, since the bloodvessels of the segment of arm within this plethysmograph were collapsed before the volume of the enclosed tissue was measured.

It was found in the normal, recumbent subject that fluid accumulated in the tissue spaces when venous pressure was greater than 15 to 20 cm. water. Above an average venous pressure of 17 cm. water the rate of filtration of fluid was directly proportional to the increase in venous pressure. A unit rise in venous pressure (1 cm. water) increased the filtration rate by 0.0023 cc. per minute per 100 cc. of arm.

The rate at which fluid was removed from the tissues of the arm depended on the size of the accumulation, being more rapid with larger collections. When the accumulated fluid amounted to less than 0.6 cc. per 100 cc. of arm the removal of fluid was retarded by elevating the venous pressure to 15 or 20 cm. water. When the accumulated fluid amounted to more than 0.6 cc. per 100 cc. of arm the fluid was removed very rapidly in spite of slight grades of venous congestion. From this it seems possible that true capillary absorption may play the dominant rôle in the removal of small accumulations of tissue fluid, while lymphatic drainage becomes more important with the larger accumulations.

When the colloid osmotic pressure of the blood was elevated by standing the rates of filtration produced by a given venous pressure were reduced below the rates observed in the same subjects when recumbent. A unit rise in colloid osmotic pressure (1 cm. water) was accompanied by a reduction in the filtration rate of from 0.0027 to 0.0045 cc. per minute per 100 cc. of arm.

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**Uric Acid in Frog's Glomerular Urine.**—J. BORDLEY, 3d, and A. N. RICHARDS (from the Physiologic Laboratory, Harvard University, School of Public Health). As a preliminary to the study of the mode of elimination of uric acid by the kidney of amphibians and reptiles, Folin's method for the quantitative estimation of this substance has been successfully adapted to such minute volumes of fluid as may be obtained by puncture of a single glomerulus of the frog's kidney. The principle of the adaptation is precisely the same as that of the original method. The reaction is conducted in a capillary tube, approximately

0.35 mm. in caliber, and the color comparison is made by the capillary tube method of Richards and Walker.

Under a low power of the microscope (15 X), on the stage of which a micrometer scale is cemented, capillary tubes are charged with columns of fluid of measured length which are successively introduced as follows: (a) Uric acid solution, 5 mm.; (b) cyanid urea solution, 5 mm.; (c) Folin's uric acid reagent, 1 mm. The tube is sealed and laid aside until the entire series, both of unknowns and standards, has been similarly prepared. When all are ready the fluids within the tubes are made to mix by whirling in a centrifuge and after an interval of 4 minutes the tubes are immersed for 1 minute in boiling water. The color comparisons are made against a brilliantly illuminated milk glass background by means of the naked eye or a reading glass.

For each series of determinations a series of 7 tubes is prepared from standard uric acid solutions as follows: 0.6, 0.8, 1.0, 1.2, 1.4, 1.6 and 2 mg. per 100 cc. If the concentration of uric acid in the unknown solution is higher than 2 mg. per 100 cc. it must be diluted appropriately to bring it into the range of the standards.

Among 39 determinations carried out in duplicate on known unknown solutions the average of the duplicates differed from the known uric acid concentration by more than 10 per cent in only 1 instance (12 per cent). The deviation from the known value was less than 5 in 74 per cent of the determinations. The average error of the 39 determinations was -1 per cent.

When 2 uric acid determinations are carried out on a single sample of glomerular urine they agree well. The technically most perfect comparisons of the uric acid content of plasma and glomerular urine collected from frogs which have been injected with uric acid indicate identity of concentration in these two fluids.

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### The Intermediate Hemoglobin Compound Hypothesis.—S. GOLDSCHMIDT (from the Physiologic Laboratory, Cambridge, England).

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# INDEX.

(In the case of original articles the page number appears in blackface type. Original articles are indexed under each author's name, and under one or more subject heads of the title; abstracted articles are less fully cross-indexed and under subject only; all book reviews are indexed singly under the head of "Reviews" according to the author's name.)

## A

- ABBOTT, A. J., blood sugar response to epinephrin in thyroid feeding, **610**
- Abdominal aorta, aneurysms of, 593  
surgery, new and simple mechanical retractor for, **43**
- Abnormalities in white blood cell response (leukemoid, atypical leukemic and leukopenic blood pictures), **334**
- Abscess, hepatic and perihepatic, use of exploring needles and shadow casting media, **421**  
perinephritic, **576**  
prostatic, **576**
- Abscesses, peritonsillar, **730**
- Achlorhydria, relation of, to pernicious anemia, **717**
- Achylia gastrica, observations on etiologic relationship of, to pernicious anemia, **IV, 741**
- Acid, uric, in frog's glomerular urine, **881**
- Adenoidotomy, evaluation of results of tonsillectomy, **579**
- Adrenal cortex in rabbit, compensatory hypertrophy of, **591**
- Age changes in inorganic constituents of sound human teeth, **152**
- Air flow, rate of, and room temperature in health of school children, **151**
- Alcohol injections, paravertebral, in angina pectoris, **282**
- Allergy, diagnostic program in food, **459**  
in middle and internal ear, **430**
- Alvarez, Walter C., problems of present-day gastroenterology, **441**
- Anderson, H. B., polypi and polypoid conditions of gastrointestinal tract, with special reference to pathologic and radiologic aspects, **177**
- Anemia, pernicious, effect of brain diet in, **717**  
observations on etiologic relationship of achylia, **741**  
relation of achlorhydria, **717**  
significance of gastric secretions in, **170**  
primary hypochromic (erythronormoblastic anemia)—new type of idiopathic anemia, **520**
- Anesthesia in treatment of fractures, use of local, **719**
- Aneurysm, aortic, rupturing into conus arteriosus of right ventricle, **208**
- Aneurysms of abdominal aorta, **593**
- Angina and intermittent claudication, muscle extract in, **577**  
pectoris, case for and against the operative treatment of, **35**  
concerning certain phases of, based on 350 cases, **784**  
glucose treatment of, **422**  
paravertebral alcohol injections in, **282**
- Animal experiments, possible clinical indications for follicular hormone therapy based upon its known biologic effect in, **326**
- Anomaly of biliary tract, unique; communications between cystic and hepatic ducts with occlusion of common duct and separate entrances into duodenum, **95**
- Antianemic influence of desiccated whole hog stomach, **319**
- "Antigens, natural bacteria," clinical observations of immunizing value of pneumococci, **454**
- Antirabic vaccine paralysis, **150**
- Antirachitic potency of milk of cows fed irradiated yeast or ergosterol, **581**
- Antitoxin, titration of scarlatinal, by means of skin test in chinchilla rabbits, **436**
- Aorta, abdominal, aneurysms of, **593**
- Aortic aneurysm rupturing into conus arteriosus of right ventricle, **208**
- Appendicitis, gangrenous, Brittain's pathognomonic sign of, **191**  
in children, **86**
- Arachnoiditis, chiasmal syndrome produced by chronic local, **290**
- Arcus senilis as an accompaniment of cardiovascular disease, **429**
- Arnett, John H., case of congenital stenosis of pulmonary valve, with late onset of cyanosis: death from carcinoma of pancreas, **212**
- Arsenic as a therapeutic agent in chronic myelogenous leukemia, **721**
- Arsenicals, organic (stovarsol and treparsol), toxicity and elimination of, in treatment of endamebiasis, **257**
- Arsphenamin, reactions of skin following intradermal injection of, **725**  
synthetic, an appraisal of newest, Bismarsen, **871**
- Arteriosclerosis and nephritis in rabbit, spontaneous, **296**

- Arteriosclerosis pituitary factor in, its experimental production in rabbits, 146
- Artery, coronary, in health and disease, 573
- pulmonary, and arterioles, sclerosis of, 297
- Arthritis deformans, rôle of streptococcus in, 682
- Artichokes, Jerusalem, and liver in treatment of diabetes mellitus, 675
- Asbestosis bodies in sputum; a study of specimens from 50 workers in an asbestos mill, 592
- pulmonary, report of case and review, 437
- Asphyxia of newborn, inhalation method of resuscitation from, 425
- Asthma, bronchial, eczema and hay fever, effect of Roentgen rays in treatment of, 869
- Astrocytomas, experiences with cerebellar, 131
- B**
- BACILLUS enteritidis infection in white mice, relation of temperature and humidity to course of, 299
- "Bacterial antigens, natural," clinical observations of immunizing value of—pneumococci, 454
- Banyai, Andrew L., pneumoperitoneum in treatment of tuberculous enterocolitis, 352
- Barach, Alvan L., immune transfusion in lobar pneumonia, 811
- Barnett, Charles W., significance of gastric secretions in pernicious anemia, 170
- Bartle, Henry J., cholagogue effect of intravenous injection of sodium dehydrocholate, with résumé of literature on bile salt metabolism, 822
- Bauer, Edward L., survey of diphtheria prevention in Philadelphia, 839
- Bauer, Walter, further studies of calcification of subcutaneous tissue ("Calcinosis Universalis") in a child, 237
- B. C. G., virulence of, effect *in vitro* of environment on, 735
- Behavior problems in children, some principles in treatment of, 589
- Bennett, Granville A., further studies in case of calcification of subcutaneous tissue ("Calcinosis Universalis") in a child, 237
- Berndt, A. L., pathogenesis of acute suppurative parotitis, 639
- Bile ducts, tumors of extrahepatic, 866
- salt metabolism, cholagogue effect of intravenous injection of sodium dehydrocholate, with résumé of literature on, 822
- Biliary tract, unique anomaly of; communications between cystic and hepatic ducts with occlusion of common duct and separate entrances into duodenum, 95
- Bilirubin, excretion of intravenously injected, as a test of liver function, 129
- Binswanger, Herbert F., Jerusalem artichokes and liver in treatment of diabetes mellitus, 675
- Birth conditions, cerebral, with special reference to cerebral diplegia, 294
- Bishop, Louis Faugères, analysis of 100 examples of cardiac pain in private practice, 19
- Bishop, Louis Faugères, Jr., analysis of 100 examples of cardiac pain in private practice, 19
- Bismarsen, newest arsphenamin synthetic, an appraisal of, in treatment for syphilis, based on 7666 injections in 341 cases during 5 years, 871
- Bismuth products, comparative excretion and absorption of different, 137
- Bladder, treatment of tumors of, 291
- Blood and hemolytotoxic system, effect of pyrocin poisoning on, 597
- cell response, abnormalities in white (leukemoid, atypical leukemic and leukopenic blood pictures), 334
- changes in leukemias and lymphomata and their bearing on Roentgen therapy, 144
- peripheral, heliotherapy and, 300
- smears from insulin-treated diabetics, percentage of eosinophils in, 231
- sugar response to epinephrin in thyroid-fed animals, 610
- transfusion, transmission of syphilis by, 720
- transfusions, effect of, on bone-marrow activity as indicated by reticulocyte count, 513
- Boas, Ernst P., rheumatic fever in adult Porto Rican immigrants, 25
- Bone-marrow activity, effect of blood transfusions on, as indicated by reticulocyte count, 513
- and spleen, Hodgkin's disease of, without apparent involvement of lymph nodes, 764
- Bone metastasis, 585
- Boothby, Walter M., creatinuria in hyperthyroidism, 476
- Brain, acute diseases of, due to functional disturbance of circulation, 293
- diet, effect of, in pernicious anemia, 717
- hemorrhage of, 876

- Brain, tumor of, with disturbance in temperature regulation, 734
- Bratley, F. G., effect of pyrodin poisoning on blood and hemolytotoxic system, 597
- Breast, carcinoma of, in young, 868  
Roentgen treatment of metastasis to vertebrae and bones of pelvis from carcinoma of, 431
- Bright's disease, renal calcification and, 736
- Britain's pathognomonic sign of gangrenous appendicitis, 191
- Broca's center, relation of, to left-handedness, 116
- Brooks, Harlow, concerning certain phases of angina pectoris based on study of 350 cases, 784
- Brower, A. Blaine, antianemic influence of desiccated whole hog stomach, 319
- Brown, Lawrason, study of 503 cases of pulmonary tuberculosis with indefinite or no usual abnormal physical signs, 700
- Brown, Philip W., toxicity and rate of elimination of organic arsenicals (stovarsol and treparsol) in treatment of endamebiasis, 257
- Buck, R., pathogenesis of acute suppurative parotitis, 639
- Burroughs, H. H., effect of pyrodin poisoning on blood and hemolytotoxic system, 597
- Buxton, R. von L., pathogenesis of acute suppurative parotitis, 639
- C**
- CALCIFICATION of subcutaneous tissue ("Calcinosis Universalis") in a child, further studies in, 237  
renal, and Bright's disease, 736
- Calcinosis, cutaneous, 582
- Calcium gluconate and other calcium salts, comparative studies on, 426
- Cancer, cervical, irradiation of, 726  
early diagnosis of cervical, 428  
of cervix, 872  
problem, present and future, 732  
Roentgen therapy of uterine, 428  
uterine, irradiation of, 287
- Capillaries, observations on living lymphatic, in rabbit, 155
- Capillary wall, movement of fluid through human, 881
- Carbohydrate metabolism in relation to postoperative crises in hyperthyroidism, 378
- Carcinoma, mammary, deep Roentgen ray therapy of, 5-year results, 143  
of breast in young, 868  
Roentgen treatment of metastasis to vertebrae and bones of pelvis from, 431
- Carcinoma of pancreas, case of congenital stenosis of pulmonary valve, with late onset of cyanosis and death from, 212  
case of diabetes mellitus and fatty diarrhea due to, 662
- Cardiac pain and sudden death, 769  
in private practice, analysis of 100 examples of, 19
- Cardiopathy, gastric, gastrocardiac syndrome, treatment of, 13
- Cardiovascular disease, arcus senilis as an accompaniment of, 429
- Carotid sinus reflexes and respiration, 154
- Cartilages, derangements of semilunar, 420
- Castle, William B., observations on etiologic relationship of achylia gastrica to pernicious anemia, IV, 741
- Cerebellar astrocytomas, experiences with, 131
- Cerebral birth conditions with reference to cerebral diplegia, 294  
complications of nephritis, treatment of acute, 426
- Cerebrospinal meningitis, eye observations in epidemic, 289
- Cerebrum, diffuse progressive degeneration of gray matter of, 733
- Cherry, Homer H., chronic basal non-tuberculous pulmonary inflammation; its etiologic significance, 367
- Chiasmal syndrome produced by chronic local arachnoiditis, 290
- Childhood, acute encephalitis during, 136
- Children, early diagnosis of rheumatic heart disease in, 870  
prognosis of acute glomerular nephritis in, 425  
pulmonary tuberculosis in, 724  
simplified treatment of empyema in, 285  
some principles in treatment of behavior problems in, 589  
treatment of postencephalitic, in a hospital school, 434
- Cholagogue effect of intravenous injection of sodium dehydrocholate, with résumé of literature on bile salt metabolism, 822
- Cholecystitis, chronic typhoid, 736
- Cholecystography, oral, necessity for accurate technique in, 730  
oral, five years' experience with, 586
- Chorea minor, for and against nirvanol treatment of, 868
- Chorea, Sydenham's, 467  
treatment of, by fever, 580
- Chronic rheumatic disease, present status of classification, pathology and etiology of, 157



- Circulatory hormone preparations, medical opinions on, 423
- Cirrhosis, infectious, 738
- Clinical application, observations on, of urine sediment count (Addis), 105
- observations of immunizing value of "natural bacterial antigens"—pneumococci, 454
- on so-called leather-bottle stomach, 847
- Clot formation, plasma, influence of ultraviolet light on, 605
- Clumsiness, disturbances in handwriting and, as signs of toxic goiter, 114
- Cod-liver oil emulsified in extract of germinating grains, 870
- Coli, melanosis, observations on, 591
- Colitis, conditions commonly called, 291
- Congenital stenosis of pulmonary valve, case of, with late onset of cyanosis: death from carcinoma of pancreas, 212
- Congo-red as a hemostypticum, 132
- Contact or patch test in dermatology, 724
- tests in dermatology, intradermal, scratch, indirect and, 286
- Conus arteriosus of right ventricle, aortic aneurysm rupturing into, 208
- Cornea, syndrome characterized by congenital clouding of, 135
- Coronary artery in health and disease, 573
- Cranial sutures, synostosis of, 722
- Creatinuria in hyperthyroidism, 476
- Custer, R. P., acute suppurative parotitis, 649
- Cutaneous calcinosis, 582
- Cyanosis, case of congenital stenosis of pulmonary valve with late onset of; death from carcinoma of pancreas, 212
- Cystin, oxidation of, by iodine, 880
- Cysts, solitary, of kidney, 719
- D**
- DAMESHEK, William, primary hypochromic anemia (erythro-normoblastic anemia), new type of idiopathic anemia, 520
- Death, sudden, and cardiac pain, 769
- Deformans, arthritis, rôle of streptococcus in, 682
- spondylitis, 575
- Dermatitis, toilet water, 286
- deVeer, J. Arnold, tuberculosis simulating acute leukemia, 372
- Dewis, E. G., interpretation of flarimeter tests, 497
- Dextrose tolerance curve, 5-hour, in treated diabetic patients, 395
- Diabetes, eye in, 873
- insulin-sensitive and insulin-resistant, 283
- mellitus and its complications; an analysis of 827 cases, 301
- case of, and fatty diarrhea due to carcinoma of pancreas, 662
- hereditary and familial, 484
- Jerusalem artichokes and liver in treatment of, 675
- Diabetic patients, 5-hour dextrose tolerance curve in treated, 395
- pyorrhea, 807
- Diabetics, a study of five hundred, 311
- insulin-treated, percentage of eosinophils in blood smears from, 231
- Diagnostic program in food allergy, 459
- Diaphragm, postoperative behavior of, 292
- Diarrhea, fatty, and diabetes mellitus, due to carcinoma of pancreas, 662
- Diet, effect of brain, in pernicious anemia, 717
- Digitalis dosage, 578
- Diphtheria, experiences with symbiotic serum in, 133
- prevention in Philadelphia, survey of, 839
- selective distribution of, 590
- toxoid as an immunizer in, 251
- Diplegia, cerebral, cerebral birth conditions with special reference to, 294
- Disks, intervertebral, 130
- Disseminated sclerosis, etiology of, 147
- Dogs, Roentgen-physiologic studies of gall bladder in, 431
- Dohrn, Max, possible clinical indications for follicular hormone therapy based upon its known biologic effect in animal experiments, 326
- Duodenal papilla, minor, variations in pancreatic ducts and, 626
- ulcer, fractional gastric analysis in 200 cases of, 719
- E**
- EAR, allergy in middle and internal, 430
- Eczema, bronchial asthma and hay fever, effect of Roentgen rays, 869
- experimental studies in, 138
- Effusion, interlobar and mediastinal encapsulated, 144
- Electrocoagulation of tonsils, present status of, 433
- Electrosurgery of tonsils, 433
- Electrosurgical destruction of recurrent lymphoid tissue after tonsillectomy, 142
- Ellis, Laurence B., studies in complete heart block; I: cardiac output and peripheral circulatory mechanism, 195

- Empyema and lung abscess, treatment of, by packing, 867  
in children, simplified treatment of, 285
- Enamel, mottled, in segregated population, 439
- Encephalitis, acute, in childhood, 136  
and encephalomyelitis in measles, 435
- Encephalographic studies in general paresis, 588
- Encephalomyelitis, disseminated, 587
- Endamebiasis, toxicity and rate of elimination of organic arsenicals (stovarsol and treparsol) in treatment of, 257
- Endocarditis, bacterial, hemorrhagic retinal lesions in (Roth's spots), 727
- Endothelial myeloma, 292
- Enterocolitis, tuberculous, pneumoperitoneum in treatment of, 352
- Enuresis, 135
- Eosinophils in blood smears from insulin-treated diabetics, 231
- Ephedrin, effect of, upon human stomach as determined roentgenologically, 387
- Epidemic, unusually mild recurring, simulating food infection, 438
- Epinephrin in thyroid-fed animals, blood sugar response to, 610
- Ergosterol, antirachitic potency of milk of cows fed, 581
- Erythema infectiosum, 872
- Etiology of disseminated sclerosis, 147
- Europe, natural disappearance of malaria, 739
- Ewing's sarcoma, 292
- Extra-pollen hypersensitivity, an important consideration in treatment of hay fever, 81
- Extravasation from ureter, 280
- Eye in diabetes, 873  
observations in epidemic meningitis, 289
- F**
- FAMILIAL and hereditary diabetes mellitus, 484
- Fatty diarrhea and diabetes mellitus, due to carcinoma of pancreas, 662
- Fever group, typhus Rocky Mountain spotted, an epidemiological and clinical study in eastern and southeastern states, 439  
rheumatic in adult Porto Rican immigrants, 25
- Flarimeter tests, interpretation of, 497
- Food allergy, diagnostic programin, 459  
infection, unusually mild recurring epidemic stimulating, 438  
poisoning: attempts to immunize human volunteers with staphylococcus filtrates, 879
- Food specific dynamic action of, in abnormal states of nutrition, 49
- Fowl-pox and Molluscum contagiosum, 737
- Fractures, use of local anesthesia, 719
- Fray, Walter W., effect of ephedrin upon human stomach as determined roentgenologically, 387
- Frazier, Charles H., carbohydrate metabolism in relation to postoperative crises in hyperthyroidism, 378
- Fremont-Smith, Maurice, guides to prevention and treatment of simpler neuroses, 261
- Friedenwald, Julius, clinical observations on so-called leather-bottle stomach, 847
- G**
- GALLAND, Walter, pseudoneoplastic luetic granulomata, 405
- Gall bladder in dogs, Roentgen-physiologic studies of, 431
- Gangrenous appendicitis, Brittain's pathognomonic sign of, 191
- Gastric analysis, fractional, in duodenal ulcer, 719  
cardiopathy, gastroduodenal syndrome, treatment of, 13  
secretions, significance of, in pernicious anemia, 170  
syphilis, 574
- Gastroenterology, problems of present-day, 441
- Gastrointestinal tract, infant, cod-liver oil tolerance by, 870  
polypi and polypoid conditions of, with special reference to pathologic and radiologic aspects, 177
- Gelfand, H. Harold, extra-pollen hypersensitivity, an important consideration in treatment of hay fever, 81
- Gentile, Antonio, unique anomaly of biliary tract; communications between cystic and hepatic ducts with occlusion of common duct and separate entrances into duodenum, 95
- Gerber, I. E., intrahepatic lithiasis, 99
- Glomerulitis, experimental acute, 280
- Glucose tolerance of rabbits, influence of ultraviolet light on, 432  
treatment of angina with, 422
- Goiter and iodine deficiency, 877  
toxic, disturbances in handwriting and clumsiness as signs of, 114
- Gold compounds, untoward results from use of, 581
- Goldring, William, observations on clinical application of urine sediment count (Addis), 105
- Gonorrheal infection in female, chronic, deep Roentgen ray treatment of, 144

- Gowan, Cecil H., rôle of streptococcus in arthritis deformans, 682  
 Granuloma, infective, 421  
 Granulomata, pseudoneoplastic luetic, 405  
 Gray, John W., rôle of streptococcus in arthritis deformans, 682

## H

- HAMILTON, D. M., effect of pyrodin poisoning on blood and hemolytotoxic system, 597  
 Handwriting, disturbances in, and clumsiness in toxic goiter, 114  
 Hare, Hobart Amory, obituary, 1e  
 Hay fever, bronchial asthma and eczema, effect of Roentgen rays, 869  
     extra-pollen hypersensitivity, 81  
 Heart block, studies in complete; I: cardiac output and peripheral circulatory mechanism, 195  
     disease, rheumatic, in children, 870  
     effect of Roentgen rays on, 586  
     in old age; study of 700 patients 75 years of age and older, 1  
 Heath, Clark W., observations on etiologic relationship of achylia gastrica to pernicious anemia, IV, 741  
 Heliotherapy and peripheral blood, 300  
 Hemoglobin compound hypothesis, intermediate, 882  
 Hemogram, value of Schilling, in otologic infections, 430.  
 Hemolysis, is osmotic an all-or-none phenomenon? 153  
 Hemolytotoxic system and blood, effect of pyrodin poisoning on, 597  
 Hemorrhage of brain, 876  
 Hemostypticum, Congo-red as a, 132  
 Hepatic and perihepatic abscess, use of exploring needles and shadow casting media in diagnosis of, 421  
 Hereditary and familial diabetes mellitus, 484  
 Herpes zoster, sodium iodide in, 427  
 Hip joint, attitudes associated with lesions about, 575  
 Hodgkin's disease of bone marrow and spleen without apparent involvement of lymph nodes, 764  
 Hog stomach, antianemic influence of desiccated whole, 319  
 Hohlweg, Walter, possible clinical indications for follicular hormone therapy based upon its known biologic effect in animal experiments, 326  
 Hormone preparations, medical opinions on circulatory, 423  
 Human stomach, effect of ephedrin upon, as determined roentgenologically, 387

- Hyperparathyroidism, experimental chronic; I: metabolism studies in man, 800  
     osteitis fibrosa cystica generalisata with, 875  
 Hypersensitiveness, studies of skin reactions in, 148  
 Hypersensitivity, extra-pollen; a consideration in treatment of, 81  
 Hypertension, retinal changes due to, 728  
 Hyperthyroidism, carbohydrate metabolism in relation to postoperative crises in, 378  
     creatinuria in, 476  
 Hypochromemia, idiopathic, 554  
 Hypochromic anemia, primary (erythro-normoblastic anemia), new type of idiopathic anemia, 520  
 Hypophrenia as symptom of juvenile paresis, 145  
 Hypotension, postural, case report, 217

## I

- Idiocy, amaurotic family, distribution of lipid in ease of Niemann-Pick's disease associated with, 296  
 Idiopathic hypochromemia, 554  
 Immigrants, rheumatic fever in adult Porto Rican, 25  
 Immune transfusion in lobar pneumonia, 811  
 Immunizing agent in diphtheria, toxoid as, 251  
     value of "natural bacterial antigens," clinical observations of pneumococci, 454  
 Impetigo contagiosa neonatorum, 424  
 India, types of insanity commonly met with in, "Indian hemp insanity," 145  
 Infancy and childhood, leukocytic reaction in tuberculosis of, blood studies with supravital technique, 221  
     interpretation of pain in, 285  
 Infantile rickets, radiation cure of, 723  
 Infants, tuberculosis in, 283  
     premature, 285  
     prevention of rickets in, 134  
     relation of infection of ear and intestinal tract in, 141  
     soft-curd milk, 581  
 Infection of ear and intestinal tract in infants, 141  
     unusually mild recurring epidemic stimulating food, 438  
     ultraviolet radiation and resistance to; intranasal infection with pneumococcus and with bacterium leprosepticum in rabbit, 595

- Infections, Schilling hemogram in otologie, 430
- Infectious cirrhosis, 738
- diseases in the Royal Navy, 279
- Inflammation, chronic basal nontuberculous pulmonary, its etiologic significance, 367
- studies on, 591
- Inhalation method of resuscitation from asphyxia of the newborn, 425
- Insanity, types of, met with in India, "Indian hemp insanity," 145
- Insulin resistance in rabbits, 153
- sensitive and insulin-resistant diabetes, 283
- treated diabetics, percentage of eosinophils in, 231
- Intermittent claudication, muscle extract in treatment of angina and, 577
- Intervertebral disks, 130
- Intestine, large, roentgenologic demonstration of polypoid lesions and polyposis of, 732
- obstruction, acute, 281
- studies on high, 281
- Intradermal injections of arsphenamin, reactions of skin following, 725
- Intragastric photography, 731
- Intrahepatic lithiasis, 99
- Intranuclear inclusions, occurrence of, in nerve cells in poliomyelitis, 878
- Iodid, sodium, in herpes zoster, 427
- Iodin deficiency and goiter, 877
- oxidation of cystin by, 880
- Iowa, infection in epidemiology of undulant fever in, 865
- undulant fever and Brucella infection in, 439
- Iron storage in splenectomized rabbits, 297
- Irradiated yeast or ergosterol, antirachitic potency of milk of cows fed, 581
- Irradiation of cervical cancer, 726
- treatment of osteogenic sarcoma by means of, 875

## J

- JAMAICA, anatomic characteristics of tuberculosis in, 437
- Jerusalem artichokes and liver in treatment of diabetes mellitus, 675
- Johnson, J. L., experimental chronic hyperparathyroidism; I: metabolism studies in man, 800
- Jones, Chester, Morse, ease of diabetes mellitus and fatty diarrhea due to carcinoma of pancreas, 662
- Juvenile paresis, hypopleremia as symptom of, 145

## K

- Kahn and positive Wassermann reactions in leprosy, 738
- Kendall, Arthur Isaac, clinical observations of immunizing value of "natural bacteria antigens"—pneumococci, 454
- Kepler, Edwin J., creatinuria in hyperthyroidism, 476
- Kern, C., effect of pyrocin poisoning on blood and hemolytopoietic system, 597
- Kidney, solitary cysts of, 719
- Koster, Harry, intrahepatic lithiasis, 99
- Krumbhaar, E. B., Hodgkin's disease of bone marrow and spleen without apparent involvement of lymph nodes, 764

## L

- LAMBERT, Alexander, cardiac pain and sudden death, 769
- La Roque, G. Paul, Brittain's pathognomonic sign of gangrenous appendicitis, 191
- Leather-bottle stomach; clinical observations on, 847
- Left-handedness, relation of Broca's center to, 116
- Leprosy, positive Wassermann and Kahn reactions in, 738
- Lesions about hip joint, attitudes associated with, 575
- Leukemia, acute monocytic (histiocytic), 716
- myelogenous, arsenic in, 721
- tuberculosis simulating acute, 372
- Leukemias and lymphomata, blood changes in, and their bearing on Roentgen therapy, 144
- Leukocytic reaction in tuberculosis of infancy and childhood; blood studies with supravital technique, 221
- Lipoid, distribution of, in case of Niemann-Pick's disease associated with amaurotic family idiocy, 296
- Lithiasis, intrahepatic, 99
- Liver and Jerusalem artichokes in treatment of diabetes mellitus, 675
- extract, intramuscular use of, 720
- in pernicious anemia and in combined system disease, 133
- function, excretion of intravenously injected bilirubin as a test of, 129
- necrosis, experimental from shale oil, 592
- tuberculosis of, 437
- Lobar pneumonia, immune transfusion in, 811

- Long, Charles-Francis, case of congenital stenosis of pulmonary valve, with late onset of cyanosis: death from carcinoma of pancreas, 212
- Lung abscess and empyema, treatment of by packing, 867
- collateral respiration in, 867
- Lymphatic capillaries, observations on living, in rabbit, 155
- Lymph nodes, Hodgkin's disease of bone marrow and spleen without apparent involvement of, 764
- Lymphoid tissue after tonsillectomy, electrosurgical destruction of recurrent, 142
- Lymphomata and leukemias, blood changes in, and their bearing on Roentgen therapy, 144
- Lymphorrhagia retinae traumatica, 729
- Lyon, B. B. Vincent, chologogue effect of intravenous injection of sodium dehydrocholate, with résumé of literature on bile salt metabolism, 822
- M**
- MACKENZIE, L. F., interpretation of fluorimeter tests, 497
- Malaria, natural disappearance of, in certain regions of Europe, 739
- Malignancy, skin, 293
- Malignant growths, palliative therapy of, 585
- Mammary carcinoma, deep Roentgen ray therapy of, 143
- Marble, Alexander, further studies in case of calcification of subcutaneous tissue ("Calcinosis Universalis") in a child, 237
- Marzullo, Eugene R., tuberculosis simulating acute leukemia, 372
- McCluggage, H. B., specific dynamic action of food in abnormal states of nutrition, 49
- Measles, convalescent serum in prophylactic treatment of, 132
- encephalitis and encephalomyelitis in, 435
- Melanosis coli, observations on, 591
- Meningitis, eye observations in epidemic cerebrospinal, 289
- Metabolism, mineral, in late rickets, 579
- Metastasis, bone, 585
- Roentgen treatment of, to vertebrae and bones of pelvis from carcinoma of breast, 431
- Milch, Henry, pseudoneoplastic luetic granulomata, 405
- Milk of cows, antirachitic potency of, fed irradiated yeast or ergosterol, 581
- Milk, soft-curd; Nature's food for infants, 581
- Miller, Joseph L., present status of classification, pathology and etiology of chronic rheumatic disease, 157
- Mills, Edward S., idiopathic hypochromemia, 554
- Mineral metabolism in late rickets, 579
- Molluscum contagiosum and fowl pox, comparison of inclusion bodies of, 737
- Morrison, Theodore H., clinical observations on so-called leather-bottle stomach, 847
- Mottled enamel in segregated population, 439
- Moxon, Gail F., diabetes mellitus and its complications; an analysis of 827 cases, 301
- Murphy, Francis D., diabetes mellitus and its complications; an analysis of 827 cases, 301
- Muscle extract in treatment of angina and intermittent claudication, 577
- Myelogenous leukemia, chronic, arsenic in, 721
- Myeloma, endothelial, or Ewing's sarcoma, 292
- Myomectomy, 139
- N**
- NEONATORUM, impetigo contagiosa, 424
- Nephritis in children, prognosis of acute glomerular, 425
- in rabbit, spontaneous arteriosclerosis and, 296
- relationship of blood uric acid content to state of renal function in, 128
- treatment of acute cerebral, complications of, 426
- Nerve cells in poliomyelitis, intranuclear inclusions in, 878
- Nerve pathways in vomiting of peritonitis, 718
- Neuroses, guides to prevention and treatment of simpler, 261
- Newborn, inhalation method of resuscitation from asphyxia of, 425
- New York schools, study of ventilation and respiratory illness in, 594
- Niemann-Pick's disease associated with amaurotic family idiocy, distribution of lipid in case of, 296
- Nirvanol treatment of chorea minor, 868
- Nutrition, specific dynamic action of food in abnormal states of, 49
- O**
- OBESITY, treatment of, with thyroxin, 577
- Obituary—Hobart Amory Hare, 1c

- O'Connor, Bernard A., new and simple mechanical retractor for abdominal surgery, 43
- Olshausen's operation, results of, 584
- Operative treatment of angina pectoris, case for and against, 35
- Oral cholecystography, necessity for accurate technique in, 730
- Organic arsenicals (stovarsol and treparsol), toxicity and elimination of, in treatment of endamebiasis, 257
- Osmotic hemolysis, is it an all-or-none phenomenon? 153
- Osteitis fibrosa cystica with hyperparathyroidism, 875
- Osteogenic sarcoma, treatment by irradiation, 875
- Osterberg, Arnold E., toxicity and rate of elimination of organic arsenicals (stovarsol and treparsol) in treatment of endamebiasis, 257
- O'Sullivan, John R., new and simple mechanical retractor for abdominal surgery, 43
- Otologic infections, value of Schilling hemogram in, 430

## P

- PAIN in infancy, interpretation of, 285
- Pancreas, carcinoma of, case of congenital stenosis of pulmonary valve, with late onset of cyanosis and death from, 212
- carcinoma of, case of diabetes mellitus and fatty diarrhea due to, 662
- Pancreatic ducts, variations in, and minor duodenal papilla, 626
- Papilla, minor duodenal, variations in pancreatic ducts and, 626
- Paralysis, antirabic vaccine, 150
- Parathyroid and thyroid glands, effect of Roentgen rays on, 144
- Paravertebral alcohol injections in angina pectoris, 282
- Paresis, general, cnecephalographic studies in, 588
- juvenile, hypophrenia as symptom of, 145
- Parotid, mixed tumors of, 432, 576
- Parotitis, acute suppurative, 649
- pathogenesis of acute suppurative, 639
- Pellagra, pathologic physiology of, 419
- Peptic ulcer, 281
- Perihepatic abscess, diagnosis of hepatic and, 421
- Perinephritic abscess, 576
- Periosteum, 576
- Peritonitis, 130
- nerve path in vomiting of, 718
- Peritonsillar abscesses, 730
- Pernicious anemia, brain diet in, 717
- and combined system disease, 133
- observations on etiologic relationship of achylia gastrica to, IV, 741
- relation of achlorhydria, 717
- significance of gastric secretions in, 170
- Pertussis, 869
- Philadelphia, survey of diphtheria prevention in, 839
- Photography, intragastric, 731
- Pituitary factor in arteriosclerosis; its experimental production in rabbits, 146
- Plasma clot formation, influence of ultraviolet light on, 605
- Pneumonia, lobar, immune transfusion in, 811
- Pneumoperitoncum in treatment of tuberculous enterocolitis, 352
- Poisoning, effect of pyrocin, on blood and hemolytotoxic system, 597
- food, attempts to immunize human volunteers with staphylococcus filtrates, 879
- Poliomyelitis, 722
- intranuclear inclusions in nerve cells in, 878
- Polypi and polypoid conditions of gastrointestinal tract, with special reference to pathologic and radiologic aspects, 177
- Polypoid lesions and polyposis of large intestine, roentgenologic demonstration of, 732
- Porto Rican immigrants, adult, rheumatic fever in, 25
- Postencephalitic children, treatment of, 434
- Postoperative behavior of diaphragm, 292
- crises in hyperthyroidism, carbohydrate metabolism in relation to, 378
- Postural hypotension, case report, 217
- Premature infants, 285
- prevention of rickets in, 134
- Prostatic abscess, 576
- Pseudoneoplastic luetic granulomata, 405
- Psittacosis: 1929-1930 outbreak in United States, 149
- Pulmonary asbestosis; report of case and review, 437
- inflammation, chronic basal non-tuberculous, its etiologic significance, 367
- tuberculosis, cavity in, 432
- in children, 724
- study of 503 cases of, with indefinite or no usual abnormal physical signs, 700

- Pulmonary tuberculosis, value of roentgenologic examination in, 584  
 Roentgen ray examination in, 143  
 valve, case of congenital stenosis of, with late onset of cyanosis and death from carcinoma of pancreas, 212  
 Pyorrhea, diabetic, 807  
 Pyrocin poisoning, effect of, on blood and hemolytopoietic system, 597

## R

- RADIATION, tungsten-filament, cure of infantile rickets with, 723  
 ultraviolet, and resistance to infection, 595  
 Radioactivity, biologic sources of, 731  
 Radium, value of, in fibroid tumors of uterus, 433  
 Ralli, Elaine P., study of 5-hour dextrose tolerance curve in treated diabetic patients, 395  
 Ray, Hartzell Harrison, toxoid as immunizing agent in diphtheria, 251  
 Reich, Carl, effect of blood transfusions on bone marrow activity as indicated by reticulocyte count, 513  
 Renal calcification and Bright's disease, 736  
 disease, cardiovascular, retinal arterial changes in, 289  
 function in nephritis, blood uric acid content, 128  
 Respiration, carotid sinus reflexes and, 154  
 collateral, in lung, 867  
 Respiratory illness and ventilation in New York schools, 594  
 ventilation, study of, in Syracuse schools, 151  
 Resuscitation from asphyxia of newborn, inhalation method, 425  
 Reticulocyte count, effect of blood transfusions on bone-marrow activity as indicated by, 513  
 Retinal changes and retinitis in cardiovascular renal disease, 289  
 changes due to hypertension and hypertonicity, 728  
 lesions, hemorrhagic, in bacterial endocarditis (Roth's spots), 727  
 Retinitis and retinal arterial changes in cardiovascular renal disease, 289  
 Retractor, new and simple mechanical, for abdominal surgery, 43  
 Reviews—  
 Ashhurst, Surgery: Its Principles and Practice, 119  
 Beckman, Treatment in General Practice, 122  
 Bell, Some Aspects of the Cancer Problem, 276

## Reviews—

- Brown, Intestinal Tuberculosis; its Importance, Diagnosis and Treatment, 412  
 Bryan, The Papyrus Ebers, 269  
 Burrell, Recent Advances in Pulmonary Tuberculosis, 862  
 Chappell, Through the Alimentary Canal with Gun and Camera, 125  
 Chittenden, Development of Physiologic Chemistry in United States, 124  
 Cole, Early Theories of Sexual Generation, 416  
 Davies, Primary Syphilis in the Female, 570  
 Declman, Surgery: A Hundred Years Ago, 415  
 DeGaris, The Theory of Obstetrics, 415  
 DeLint, Rembrandt, 712  
 Dessauer, Zehn Jahre Forschung auf dem Physikalisch-medizinischen Grenzgebiet, 568  
 Diergart, Proteus, Band I; Festgabe für Wilhelm Haberling, 274  
 Eckstein, Noguchi, 860  
 Fishberg, Hypertension and Nephritis, 566  
 Fulton, Physiology, Vol. V of Clio Medica, 268  
 Gager, Hypertension, 709  
 Geneeskundige Kunstkalender—Voor Het Jaar 1931, 713  
 Ivy and Curtis, Fractures of the Jaws, 859  
 Jellinek, Der Elektrische Unfall, 416  
 Kaplan, Practical Radiation Therapy, 273  
 Kessler, Accidental Injuries, 566  
 Kohn, Practical Treatise on Diseases of the Digestive System, Vols. I and II, 273  
 Lewis, Clinical Electrocardiography, 712  
 McMurrick, Leonardo da Vinci: The Anatomist, 120  
 Miller, An Introduction to Gynecology, 862  
 Munch, Bioassays—Handbook of Quantitative Pharmacology, 274  
 Papers and Speeches of John Chalmers Da Costa, 272  
 Peters and Van Slyke, Quantitative Clinical Chemistry, Vol. I—Interpretations, 275  
 Plunkett, Outlines of Modern Biology, 270  
 Power, Selected Writings 1877-1930, 122  
 Roberts, Eye, Ear, Nose and Throat for Nurses, 713

## Reviews—

- Rowe, Food Allergy, 412  
 Sachs, The Diagnosis and Treatment of Brain Tumors, 570  
 Schilder, Nervous and Mental Disease Monograph, Series No. 53, Brain and Personality, 414  
 Simkins, Textbook of Human Embryology, 277  
 Smith, Significance of The Peking Man, 272  
 Snow, Textbook of Physical Therapy, Vol. I, 860  
 Stieglitz, Arterial Hypertension, 268  
 Still, The History of Pædiatrics, 568  
 Stockard, The Physical Basis of Personality, 710  
 Strecker and Appel, Discovering Ourselves, 567  
 Stubbs and Bligh, Sixty Centuries of Health and Physick, 708  
 System of Bacteriology in Relation to Medicine, Vol. II, Cocci, Hemophilic Bacteria, 270  
 System of Bacteriology in Relation to Medicine, Vol. V, Glanders, Diphtheria, Tuberculosis, Leprosy, Brucella, Anthrax, 271  
 System of Bacteriology in Relation to Medicine, Vol. VII, Virus Diseases, Bacteriophage, 121  
 Tendeloo, Studien ueber die Entstehung und den Verlauf der Lungenkrankheiten, 709  
 Thomson and Thomson, The Pathogenic Streptococci, Monograph XI, The Rôle of the Streptococci in Scarlet Fever, 269  
 Todd, Easier Motherhood, 710  
 Urban, Die Chirurgie des Kropfes, 413  
 Warburg, Metabolism of Tumors, 123  
 Warthin, The Physician of the Dance of Death, 569  
 Weiss, Thomas Say, Early American Naturalist, 120  
 Wenckebach, Medizinische Praxis, Vol. XII: Herz- und Kreislauf-Insuffizienz, 711  
 Williamson, Diseases of Children, 276  
 Winslow, Health on the Farm and in the Village, 860  
 Zinsser, Resistance to Infectious Diseases, 712
- Rheumatic disease, chronic, present status of classification, pathology and etiology of, 157  
 fever in adult Porto Rican immigrants, 25
- Rheumatic heart disease in children, early diagnosis of, 870  
 Rickets, cure of infantile, with tungsten-filament radiation, 723  
 mineral metabolism in late, 579  
 prevention of, in premature infants, 134  
 Rocky Mountain spotted fever type, an infection of, 879  
 Roemheld, L., treatment of gastrocardiac syndrome (gastric cardiopathy), 13  
 Roentgenologic appearance of interlobar and mediastinal encapsulated effusion in thorax, 144  
 changes in sarcoid and related lesions, 585  
 examination in pulmonary tuberculosis, 584  
 Roentgen-physiologic studies of gall bladder in dogs, 431  
 Roentgen ray examination in pulmonary tuberculosis, 143  
 therapy, deep, of mammary carcinoma, 143  
 treatment, deep, of chronic gonorrheal infection in female, 144  
 rays, in treatment of bronchial asthma, eczema and hay fever, 869  
 effects of, on healing of wounds, 293  
 on heart, 586  
 on thyroid and parathyroid glands, 144  
 therapy, blood changes in leukemias and lymphomata and their bearing on, 144  
 of uterine cancer, 428  
 treatment of metastasis to vertebrae and bones of pelvis from carcinoma of breast, 431  
 Room temperature and rate of air flow, in relation to health of school children, 151  
 Rosenblum, Albert, observations of immunizing value of "natural bacterial antigens"—pneumococci, 454  
 Rothschild, Karl, relation of Broca's center to lefthandedness, 116  
 Roth's spots, hemorrhagic retinal lesions in bacterial endocarditis, 727  
 Royal navy, distribution of infectious diseases in, 279  
 Ruptures, tendon, observations on, 718

## S

- SALPINGOGRAPHY, 727  
 Salpingostomy, 288  
 Sanders, Audley O., postural hypotension, case report, 217



- Sanders, C. B., aortic aneurysm rupturing into conus arteriosus of right ventricle, 208
- Sarcoid and related lesions, roentgenologic changes in, 585
- Sarcoma, Ewing's, endothelial myeloma or, 292  
irradiation treatment of osteogenic, 875
- Scarlatinal antitoxin, titration of, by means of skin test in chinchilla rabbits, 436
- Schilling hemogram in otologic infections, 430
- Schoeller, Walter, possible clinical indications for follicular hormone therapy based upon its known biologic effect in animal experiments, 326
- School children, rate of air flow and room temperature in relation to health of, 151
- Schwab, Edward H., aortic aneurysm rupturing into conus arteriosus of right ventricle, 208
- Sclerosis, etiology of disseminated, 147  
of pulmonary artery and arterioles, 297
- Semilunar cartilages, derangements of, 420
- Semon's law, observations on, 141
- Serum, convalescent, in prophylactic treatment of measles, 132  
symbiotic, experiences with, in diphtheria, 133
- Sevringhaus, Elmer L., study of 500 diabetics, 311
- Shale oil, experimental liver necrosis from, 592
- Shannon, James, study of 5-hour dextrose tolerance curve in treated diabetic patients, 395
- Sigmoid, transplantation of ureters to, 131
- Simkins, Samuel, variations in pancreatic ducts and minor duodenal papilla, 626
- Simpson, Walter M., antianemia influence of desiccated whole hog stomach, 319
- Sinus, carotid, and respiration, 154
- Sinusitis, histopathology and bacteriology of, 431
- Skin malignancy, 293  
reactions, studies of, in hypersensitivity, 148  
test in chinchilla rabbits, titration of scarlatinal antitoxin by means of, 436
- Skiodan, urinary tract roentgenography by means of, 292
- Smith, Carl H., leukocytic reaction in tuberculosis of infancy and childhood; blood studies with supravital technique, 221
- Sodium dehydrocholate, cholagogue effect of intravenous injection of, with résumé of literature on bile salt metabolism, 822  
iodid in herpes zoster, 427
- Soskin, Samuel, Jerusalem artichokes and liver in treatment of diabetes mellitus, 675
- Spleen and bone marrow, Hodgkin's disease of, without apparent involvement of lymph nodes, 764
- Splenectomized rabbits, iron storage in, 297
- Spondylitis deformans, 575
- Spotted fever type, Rocky Mountain, and infection of, 879
- Sputum, asbestosis bodies in, 592
- Stenosis, congenital, of pulmonary valve with late cyanosis; death from carcinoma of pancreas, 212
- Sterilization, operation for, 583
- Sterner, Robert F., cholagogue effect of intravenous injection of sodium dehydrocholate, with a résumé of literature on bile salt metabolism, 822
- Stillbirth problem in United States, 740
- Stomach, effect of ephedrin upon human, as determined roentgenologically, 387
- Stovarsol and treparsol, organic arsenicals, toxicity and rate of elimination of, in treatment of endamebiasis, 257
- Strang, J. M., specific dynamic action of food in abnormal states of nutrition, 49
- Strauss, Maurice B., observations on etiologic relationship of achylia gastrica, 741
- Streptococcus in arthritis deformans, rôle of, 682
- Stridor, chronic, in childhood, sometimes erroneously attributed to enlargement of thymus, 135
- Strouse, Solomon, Jerusalem artichokes and liver in treatment of diabetes mellitus, 675
- Studies, experimental, in eczema, 138
- Sutton, Don C., clinical observations of immunizing value of "natural bacterial antigens"—pneumococci, 454
- Sutures, cranial, synostosis of, 722
- Sydenham's chorea, 467
- Symbiotic serum in diphtheria, 133
- Synostosis of cranial sutures, 722
- Syphilis, cutaneous and mucosal relapse in early, 427  
gastric, 574  
newest arsphenamin synthetic, bismarsen, in treatment for, 871  
transmission of, by blood transfusion, 720  
25 years' study and survey of, 421

Syracuse schools, study of ventilation and respiratory illness in, 151

## T

TASCHE, Leslie W., appendicitis in children, 86

Teeth, age changes in inorganic constituents of sound human, 152

Temperature and humidity, relation of, to course of bacillus enteritidis infection, 299

regulation, tumor of brain with disturbance in, 734

Tendon ruptures, observations on, 718

Therapy, deep Roentgen ray, of mammary carcinoma, 5-year results, 143

palliative, of malignant growths, 585

possible clinical indications for follicular hormone, based upon its known biologic effect in animal experiments, 326

Roentgen, of uterine cancer, 428

Thompson, William P., abnormalities in white blood cell response (leukemoid, atypical leukemic and leukopenic blood pictures), 334

Thorax, roentgenologic appearance of interlobar and mediastinal encapsulated effusion in, 144

Thymus, stridor in childhood, 135

Thyroid and parathyroid glands  
Roentgen rays on, 144

Thyroidectomy, effect of, on response to insulin: spontaneous insulin resistance in rabbits, 153

Thyroid-fed animals, blood sugar response to epinephrin in, 610

Thyroxin, treatment of obesity, 577

Tick-bite fever virus to guinea pigs, transmissibility of, 297

Tobacco, toxic manifestations of, 283

Tonsillectomy and adenoidotomy, results of, 579

electrosurgical destruction of recurrent lymphoid tissue after, 142

Tonsils, electrosurgery of, 433

electrocoagulation of, 433

Tovell, Harold M., polypi and polypoid conditions of gastrointestinal tract, with special reference to pathologic and radiologic aspects, 177

Toxic goiter, disturbances in handwriting and clumsiness in, 114

manifestations of tobacco, 283

Toxicity and rate of elimination of organic arsenicals (stovarsol and treparsol) in treatment of endamebiasis, 257

Toxoid as immunizing agent in diphtheria, 251

Transfusion, immune, in lobar pneumonia, 811

Transfusions, effect of blood, on bone-marrow activity as indicated by reticulocyte count, 513

Transplantation of ureters to sigmoid, 131

Treparsol and stovarsol, organic arsenicals, toxicity and rate of elimination of, in treatment of endamebiasis, 257

Trewhella, Arthur P., case for and against the operative treatment of angina pectoris, 35

Tubercle bacilli, found in tuberculous lesions and in nontuberculous tissue in man, 298

Tuberculosis, cavity in pulmonary, 432  
in infancy and childhood, leukocytic reaction in, blood studies with supravital technique, 221

in infants and children, 283

in Jamaica, anatomic characteristics of, 437

of liver, 437

pulmonary, in children, 724

roentgenologic examination in, 584

Roentgen ray examination in, 143

simulating acute leukemia, 372

studies on; relation of tubercle and monocyte-lymphocyte ratio to resistance and susceptibility in tuberculosis, 593

study of 503 cases of pulmonary, with indefinite or no usual abnormal physical signs, 700

Tuberculous enterocolitis, pneumoperitoneum in treatment of, 352

Tumor of brain with disturbance in temperature regulation, 734

Tumors, mixed, of parotid, 432, 576

of bladder, treatment of, 291

of extrahepatic bile ducts, 866

of uterus, radium in treatment of fibroid, 433

Tungsten-filament radiation, cure of infantile rickets with, 723

Typhoid cholecystitis, chronic, 736

fever, water-borne, 596

vaccine, study of effect of, 439

Typhus-Rocky Mountain spotted fever group, 439

## U

ULCER, duodenal, fractional gastric analysis in, 719

peptic, 281

Ultraviolet light, influence of, on glucose tolerance of rabbits, 432

- Ultraviolet light, influence of, on plasma clot formation, 605  
 Vaccination and resistance to infection, 595
- Undulant fever, infection in epidemiology of, 865  
 studies of, 299
- Ureter, extravasation from, 280
- Urethra, transplantation of, 131
- Uric acid in frog's glomerular urine, 881
- Urographic tract roentgenography by means of skioidan, 292
- Urine sediment count (Addis), observations on clinical application of, 105
- U'my, Thomas Van Orden, case of diabetes mellitus and fatty diarrhea due to carcinoma of pancreas, 662
- Urography, intravenous, 586  
 and uroselectan, 143
- Uroselectan, intravenous urography and, 143
- Uterine cancer, irradiation of, 287  
 roentgen therapy of, 428  
 hemorrhage without demonstrable pathology, 291
- Uterus, radium in, fibroid tumors of, 433
- V**
- Vaccine paralysis, antirabic, 150  
 effect of typhoid, when given after infection, 439
- Van Buskirk, F. W., blood sugar response to epinephrin in thyroid-fed animals, 610
- Vanden Berg, Henry J., disturbances in handwriting and clumsiness as signs of toxic goiter, 114
- Vaughan, Warren T., diagnostic program in food allergy, 459
- Ventilation and respiratory illness in New York schools, 594  
 in Syracuse schools, 151
- Vioosterol 100-D, prevention of rickets in premature infants by use of, 134
- Vogelaar, Johannes P. M., influence of ultraviolet light on plasma clot formation, 605
- W**
- WAGGONER, R. W., Sydenham's chorea, 467
- Wartman, William B., influence of ultraviolet light on plasma clot formation, 605
- Wassermann, positive, and Kahn reactions in leprosy, 738
- Watson, E. M., percentage of eosinophils in blood smears from insulin-treated diabetics, 231
- Weiss, Soma, studies in complete heart block; I: cardiac output and peripheral circulatory mechanism, 195
- Wells, P. V., interpretation of flarimeter tests, 497
- Wildner, R. M., experimental chronic hyperparathyroidism; I: metabolism studies in man, 800
- Williams, J. B., diabetic pyorrhea, 807
- Willius, Fredrick A., heart in old age; study of 700 patients 75 years of age and older, 1
- Wood, Josephine Colburn, case of diabetes mellitus and fatty diarrhea due to carcinoma of pancreas, 662
- Wounds, effect of Roentgen rays on healing of, 293
- Wright, Irving Sherwood, hereditary and familial diabetes mellitus, 484
- Y**
- YATER, Wallace M., case for and against operative treatment of angina pectoris, 35
- Yeast, irradiated, antirachitic potency of milk of cows fed, 581
- Ylvisaker, L. S., interpretation of flarimeter tests, 497

